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SYNTHETIC STRATEGY TO NEW TERPHENYL-TYPE BIS-PYRROLE ARENES STARTING FROM HIGHLY ELECTRON-DEFICIENT 4-NITROANILINES WITH 1,4-DIKETONES

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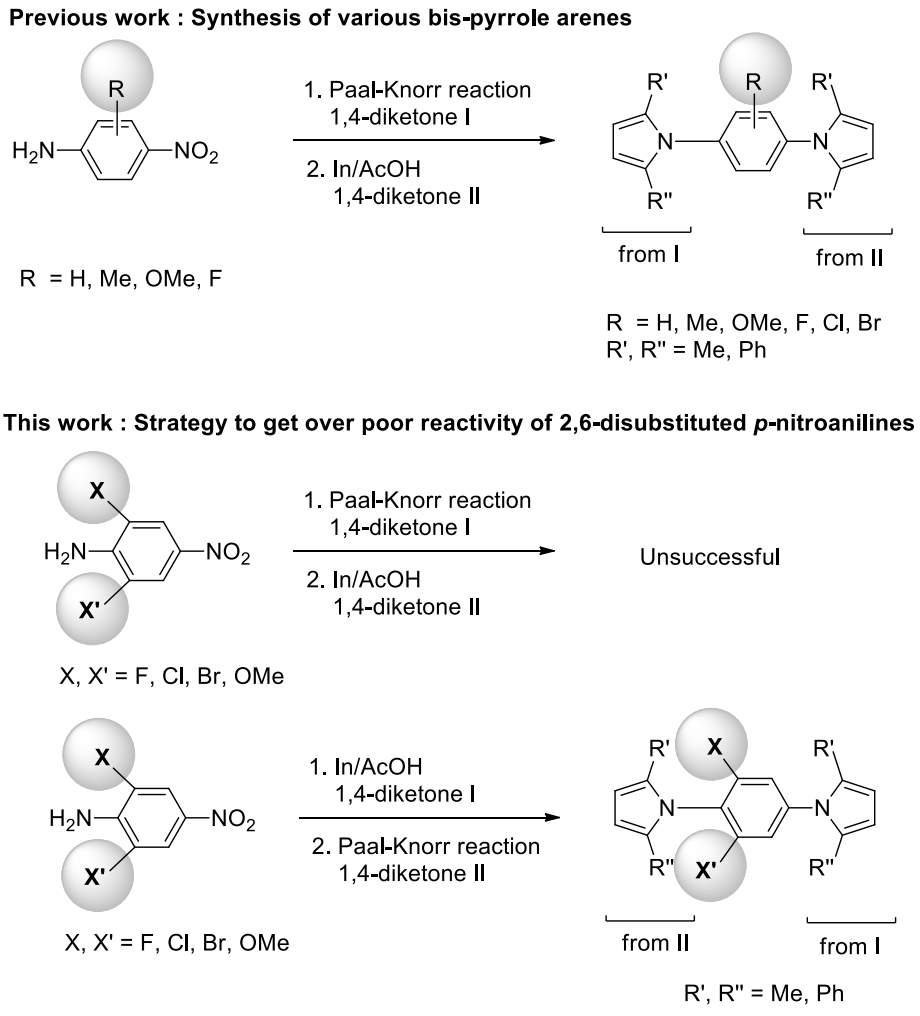
Abstract – A new synthetic method for converting highly electron-deficient 4-nitroanilines into terphenyl-type bis-pyrrole arene derivatives has been developed, which is not easy to accomplish using conventional methods because of their poor reactivity. This process involves an indium-mediated reductive cyclization reaction of highly electron-deficient 2,6-disubstituted nitroanilines in the presence of a 1,4-diketone to form 2,6-disubstituted 4-(1*H*-pyrrol-1-yl)anilines followed by cyclization with another 1,4-diketone to give the target bis-pyrrole arene products in moderate to high yield.

Indium-mediated reductive cyclization reactions have been widely studied and applied toward the preparation of five- and six-membered *N*-heterocyclic compounds such as benzoxazoles,[1] benzimidazoles,[2] benzopyrroles,[3] and quinoxalines,[4] and proceed via the single electron donation ability of indium. Among these *N*-heterocyclic compounds, pyrrole derivatives are found in a wide range of natural products[5] and bioactive molecules that exhibit versatile biological activities including anti-inflammatory and immunosuppressant properties.[6] In addition, polypyrrole derivatives are used in conducting organic polymer films due to their electrochemical properties.[7] In the case of these extended pyrrole derivatives, the synthetic methods used for their preparation and advantages of pyrrole-substituted arenes such as terphenyl-type bis-pyrrole arenes have been rarely reported.[8] The conventional Paal–Knorr condensation reaction using an amine and 1,4-diketone is a good method for the synthesis of pyrroles and can be used to prepare a diverse range of terphenyl-type bis-pyrrole arene derivatives.

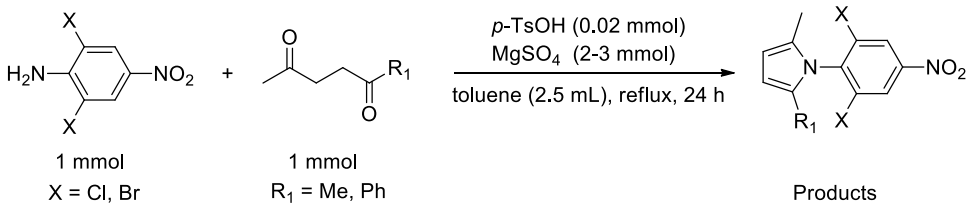
We have recently reported a facile and efficient approach to a variety of arene derivatives bearing two

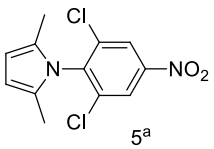
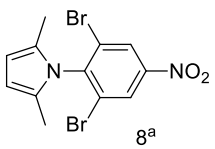
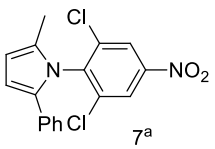
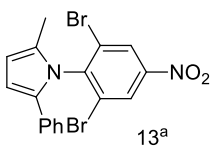
distinct pyrrole groups starting from nitroanilines using a sequential two-step reaction, i.e., Paal–Knorr reaction followed by indium-mediated reductive cyclization (Scheme 1).[9] After the success of this sequential two-step reaction, we attempted to extend it to highly electron-deficient nitroanilines such as 2,6-dihalosubstituted 4-nitroanilines to give versatile terphenyl-type arenes. However, the Paal-Knorr reaction step was unsuccessful. The strong inductive and steric effects of the 2,6-dihalogen substituents and the resonance effect of the nitro group on the phenyl ring may strongly interfere with the *N*-heterocyclization reaction between the amino group and 1,4-diketone. Fortunately, formation of the electron-deficient arene derivatives bearing two target pyrrole groups can be accomplished by changing the reaction order used in this previous study. Thus, we developed a simple and useful two-step protocol for the synthesis of symmetric and asymmetric terphenyl-type arenes containing highly electron-deficient substituents using an indium reductive-mediated cyclization reaction followed by the Paal–Knorr condensation reaction.



Scheme 1

As mentioned above, we attempted to obtain the electron-deficient arene derivatives bearing two target pyrrole groups using the previously developed two-step reaction, i.e., Paal–Knorr reaction followed by indium-mediated reductive cyclization. When the reaction was carried out using highly electron-deficient 2,6-dihalosubstituted nitroanilines (1 mmol) and 1,4-diketones (1 mmol) in the presence of *p*-TsOH (0.02 mmol) and $MgSO_4$ (2-3 mmol) under reflux for 24 h in toluene (2.5 mL), the corresponding products were obtained in poor yield (5–13%). These results indicate that the reactivity of 2,6-dihalosubstituted nitroanilines with 1,4-diketones was significantly decreased in the Paal–Knorr condensation reaction because of the electron-withdrawing properties of the nitro group and the steric and inductive effects of the 2,6-dihalogen groups on the phenyl ring. Thus, our previously developed synthetic strategy used for the synthesis of terphenyl-type bis-pyrrole arenes was not applicable to substrates bearing highly electron-deficient substituents.



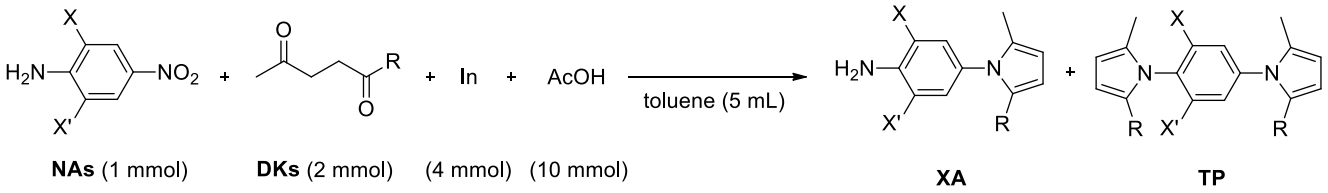
Products			
			
5[a]	8[a]	7[a]	13[a]

[a] Isolated yield.

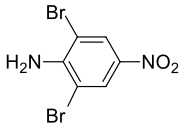
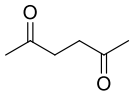
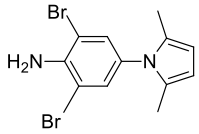
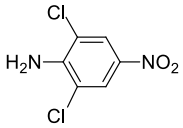
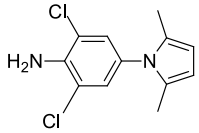
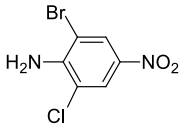
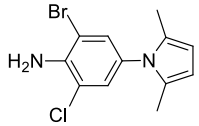
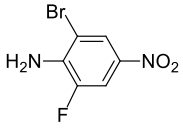
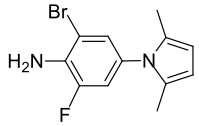
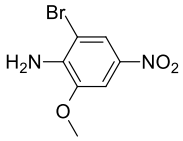
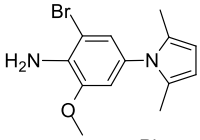
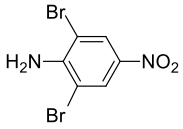
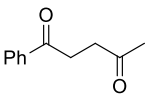
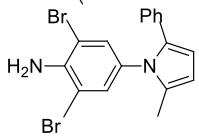
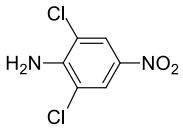
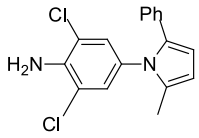
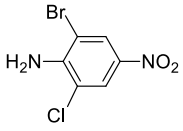
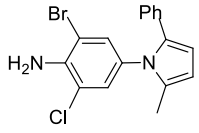
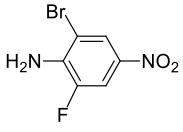
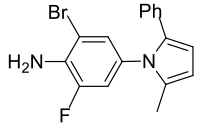
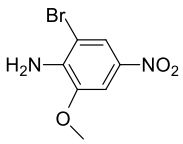
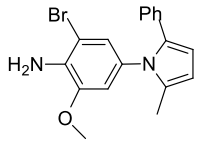
Scheme 2

To overcome this poor reactivity, we designed a new synthetic strategy to synthesize the target electron-deficient 2,6-dihalosubstituted terphenyl-type bis-pyrrole arene derivatives. For this purpose, we decided to carry out the reductive cyclization reaction as the first step because the 4-amino group formed in situ was expected to be more reactive than the 1-amino group in the starting material, which is highly-electron deficient and sterically hindered by the 2,6-dihalogen substituents. The Paal–Knorr condensation reaction with the second 1,4-diketone may then be carried out to form the desired symmetric/asymmetric terphenyl-type bis-pyrrole arene product by appropriately controlling the reaction conditions. Consequently, various pyrrole ring-containing 2,6-disubstituted anilines (**XAs**) were obtained as an intermediate product using indium (4 mmol) as a single electron transfer (SET) reagent and AcOH (10 mmol) under co-activation conditions in moderate to good yield (77–89%) starting from 2,6-disubstituted nitroanilines (**NAs**, 1 mmol) and hexane-2,5-dione (2 mmol) (Table 1, entries 1–5).

Table 1. Indium-mediated reductive *N*-heterocyclization of various 2,6-disubstituted nitroanilines



NAs (1 mmol) **DKs** (2 mmol) (4 mmol) (10 mmol) **XA** **TP**

Entry	NAs	DKs	Temp (°C)	Time (h)	Product		Yield (%)[a] XA	TP
1			80	6		**1**	88	2
2			80	12		**2**	89	2
3			80	12		**3**	88	4
4			80	12		**4**	77	8
5			80	12		**5**	84	5
6			reflux	8		**6**	63[b]	2
7			reflux	12		**7**	67[b]	2
8			reflux	12		**8**	82	14
9			reflux	12		**9**	82	11
10			reflux	12		**10**	85	5

[a]Isolated yield.

[b]Substrate was remained.

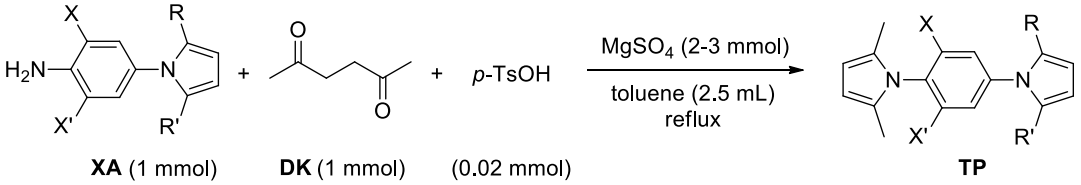
During the indium-mediated reductive cyclization reaction, **XA** was obtained as the major product, however, a small amount of **TP** was produced as a by-product in 2–14% yield (entries 1–10), as expected. These results show that the reactivity of the 4-amino group formed from the nitro group is higher than the 1-amino group in the *N*-heterocyclization reaction. In addition, symmetric (entries 6 and 7) and asymmetric (entries 8–10) 2,6-dihalosubstituted nitroanilines react with 1-phenylpentane-1,4-dione to give their corresponding products (**6**–**10**) in 63–85% yield.

After the successful preparation of a variety of 2,6-dihalosubstituted 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)anilines (**XA**), which can be expected to be converted into their corresponding terphenyl-type bis-pyrrole arenes (**TP**), we examined the Paal–Knorr condensation reaction between **XA** and hexane-2,5-dione (**DK**) using *p*-TsOH (0.02 mmol) as an acid catalyst and $MgSO_4$ (2–3 mmol) as a dehydration reagent for 12 h under reflux in toluene (2.5 mL) (Table 2). The reaction of **XA** with **DK** produced the symmetrical bis-pyrrole-containing 2,6-dihalosubstituted arene products in 15, 22, and 13% yields (41, 55, and 59% conversion), respectively (entries 1–3). Even though the reactions showed relatively low conversions (40–60%), the results were more effective when compared to our previous Paal–Knorr reaction followed by indium-mediated reductive cyclization strategy. In addition, the reaction of 2-bromo-6-fluoro-substituted and 2-bromo-6-methoxy-substituted 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)anilines (**4** and **5**) with **DK** produced 1,1'-(2-bromo-6-fluoro-1,4-phenylene)bis(2,5-dimethyl-1*H*-pyrrole) and 1,1'-(2-bromo-6-methoxy-1,4-phenylene)bis(2,5-dimethyl-1*H*-pyrrole) in 63 and 88% yields (83 and 90% conversion), respectively (entries 4–5). Similar reactions were examined using 2,6-disubstituted 4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)anilines prepared from **NAs** and 1-phenylpentane-1,4-dione (entries 6–10). The reactions afforded products **16**–**20** in 14–77% yield (37–92% conversion), which showed a similar trend to the reactions performed using **NAs** and **DK**. We believe the high yield obtained for **14**, **15**, **19**, and **20** are very promising results for the development of new terphenyl-type bis-pyrrole arene derivatives.

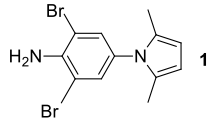
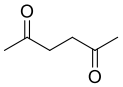
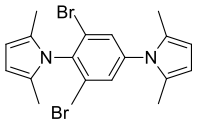
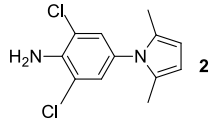
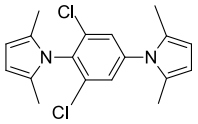
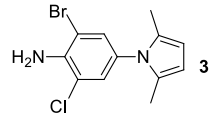
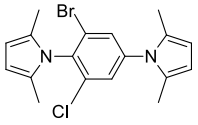
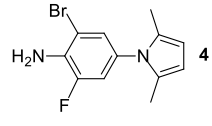
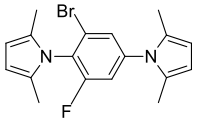
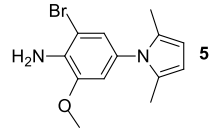
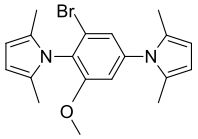
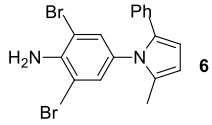
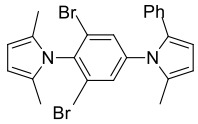
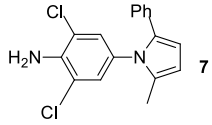
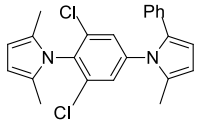
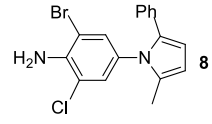
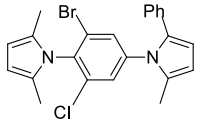
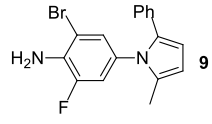
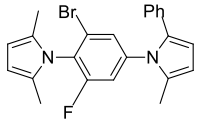
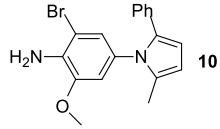
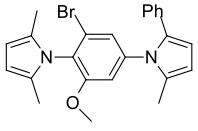
Thus, our proposed strategy to synthesize highly electron-deficient terphenyl-type bis-pyrrole heterocyclic compounds (**TPs**) was proven to work in moderate to high yield starting from highly electron-deficient 2,6-disubstituted nitroanilines (**NAs**) using 1,4-diketones (Scheme 3). The nitro group in **NA** is initially converted into an amino group via a sequential SET reaction/reduction reaction using indium/AcOH. As a result, **NA** is transformed into the 2,6-disubstituted benzene-1,4-diamine (**DA**) intermediate, which can be used as a precursor to the target *N*-heterocyclic product upon reaction with **DK2** *via* a Paal–Knorr condensation reaction. The reactivity of **DA** containing two amino groups with **DK1** in the *N*-heterocyclization reaction shows the reaction is regioselective. Due to steric and inductive effects, the amino group at site B in **DA** exhibits enhanced reactivity when compared to the amino group at site A. As a result, **XA** is preferentially generated via the condensation reaction with **DK1** at site B.

Subsequently, the amino group at site A is converted to pyrrole upon reaction with **DK2**.

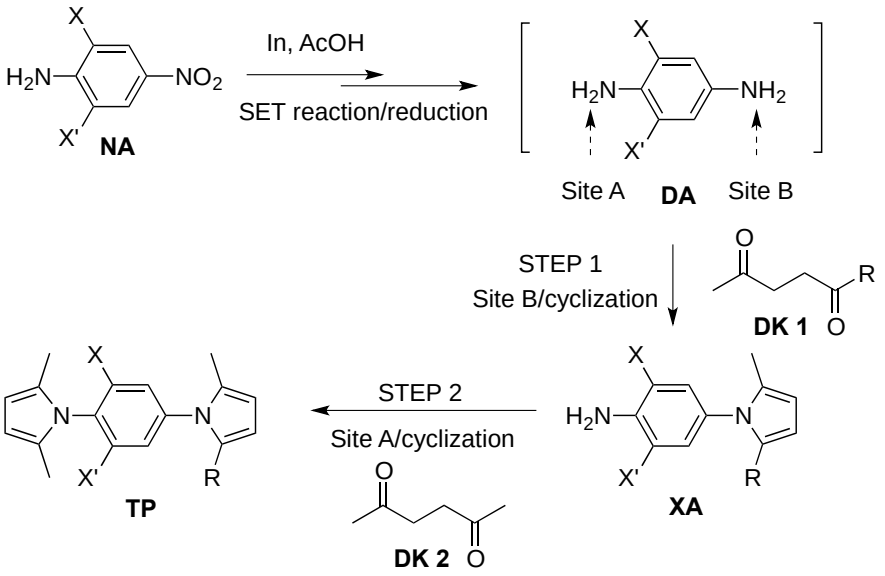
Table 2. Paal-Knorr reaction of 2,6-disubstituted (1*H*-pyrrol-1-yl)anilines



XA (1 mmol) **DK** (1 mmol) (0.02 mmol) **TP**

Entry	XA	DK	Time (h)	Product	Yield (%)[a]
1	 **1**		12	 **11**	15[b] (41)[c]
2	 **2**		12	 **12**	22[b] (55)[c]
3	 **3**		12	 **13**	13[b] (59)[c]
4	 **4**		12	 **14**	63 (83)[c]
5	 **5**		12	 **15**	88 (90)[c]
6	 **6**		12	 **16**	32[b] (64)[c]
7	 **7**		12	 **17**	36 (88)[c]
8	 **8**		12	 **18**	14[b] (37)[c]
9	 **9**		12	 **19**	67 (89)[c]
10	 **10**		12	 **20**	77 (92)[c]

[a]Isolated yield.
[b]Starting aniline substrate was recovered mostly.
[c]Conversion yield (%).



Scheme 3

On the basis of this proposed mechanism, the synthesis of electron-deficient 2,6-disubstituted heterocyclic derivative **TP** was based on the regioselective reaction of the amino groups controlled by both steric and inductive effects.

In this paper, we have demonstrated a new synthetic strategy for the formation of diverse bis-pyrrole arenes from electron-deficient 2,6-disubstituted nitroanilines and 1,4-diketones using an indium-mediated reductive cyclization reaction followed by a Paal–Knorr condensation reaction. Based on our previously reported study, we found the main drawback in the reaction was that the amino group exhibits poor reactivity in the Paal–Knorr reaction due to the presence of the highly electron-deficient substituents on the phenyl ring in the starting material. Interestingly, the poor reactivity of electron-deficient 2,6-disubstituted nitroanilines was improved using a sequential 2-step reaction involving the indium-mediated reductive cyclization and Paal–Knorr reactions. This protocol not only forms symmetric and asymmetric terphenyl-type heterocyclic derivatives, but also highly electron-deficient 2,6-disubstituted terphenyl-type heterocyclic compounds in moderate to high yield.

EXPERIMENTAL

1. General consideration

Most chemical reagents were purchased from Sigma-Aldrich Co. (St. Louis, Missouri, USA) and were used as-received without any further purification. All solvents were dried using standard methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively (JEOL, Tokyo, Japan). Chemical shifts are reported in parts per million (ppm) relative to the residual solvent or TMS as an internal standard. GC–MS spectra were recorded on an Agilent 6890N GC connected to an Agilent 5975 mass selective

detector (Hewlett-Packard Co., Palo Alto, California, USA). Infrared (IR) spectra were recorded using an MB104 FTIR spectrometer (ABB Bomem, Inc., Zurich, Switzerland). Elemental analysis was carried out on a Thermo Scientific Flash 2000 instrument (Thermo Fisher Scientific, USA). Melting points were determined on an electrothermal apparatus and were uncorrected. All the major products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, Merck & Co., Inc., Whitehouse Station, New Jersey, USA) using ethyl acetate/hexane as the eluent.

2. General procedure for the indium-mediated reductive reaction of 2,6-disubstutited nitroanilines with 2,5-hexanedione or 1-phenyl-1,4-pentanedione to obtain 4-(1*H*-pyrrol-1-yl)aniline derivatives

To a mixture of the 2,6-dihalo-4-nitroaniline derivative (1.0 mmol) and indium powder (459 mg, 4.0 mmol) in toluene (2.5 mL) was added acetic acid (573 μL, 10 mmol) followed by the 1,4-diketone (2.0 mmol) in toluene (2.5 mL). The resulting mixture was stirred at 80 °C (2,5-hexanedione) or reflux (1-phenyl-1,4-pentanedione) under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with EtOAc (30 mL) or CH_2Cl_2 (30 mL) and filtered through a celite pad. The filtrate was poured onto a 10% aqueous solution of $NaHCO_3$ (30 mL), the layers separated, and the aqueous layer extracted with EtOAc (30 mL × 3) or CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified using flash column chromatography on neutral silica gel eluted with EtOAc/hexane (v/v = 5/95) to give the corresponding pyrrole product. The structures of the pyrrole products, which were mostly novel compounds, were characterized using ^{1}H NMR, ^{13}C NMR and FTIR spectroscopy, GC–MS, and HRMS.

2,6-Dibromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline (1). Yield 88%. White solid, mp 112-113 ºC. TLC (30% EtOAc/hexane) R_f 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 2H), 5.84 (s, 2H), 4.67 (s, 2H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 131.5, 129.8, 107.8, 105.6, 12.9; IR 3464, 3356, 3059, 2974, 1612, 1574, 1481, 1408, 1273 cm^{-1}; GC-MS *m/z* (rel intensity) 342 (M^+, 100), 327 (7), 261 (7), 247 (14), 171(20), 154 (12), 123 (8); HRMS *m/z* calc. for $C_{12}H_{12}N_2Br_2$ 341.9367, found 341. 9391.

2,6-Dichloro-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline (2). Yield 89%. White solid, mp 111-112 ºC. TLC (30% EtOAc/hexane) R_f 0.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 5.84 (s, 2H), 4.55 (s, 2H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ139.7, 128.9, 128.9, 127.7, 105.6, 12.9; IR 3068, 3356, 3055, 2985, 1612, 1582, 1489, 140, 1276 cm^{-1}; GC-MS *m/z* (rel intensity) 254 (M^+, 100), 239 (16), 218 (19), 178(54), 143 (21), 124 (15); HRMS *m/z* calc. for $C_{12}H_{12}N_2Cl_2$ 254.0378, found 254.0342.

2-Bromo-6-chloro-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline (3). Yield 89%. White solid. mp 113-114 ºC.

TLC (30% EtOAc/hexane) R_f 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 1H, J = 2.2 Hz), 7.12 (d, 1H, J = 2.2 Hz), 5.85 (s, 2H), 4.67 (s, 2H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 130.8, 129.5, 128.9, 128.4, 118.6, 108.3, 105.7, 12.8; IR 3460, 3367, 3057, 2930, 1628, 1578, 1493, 1433, 1406 cm^{-1}; GC-MS *m/z* (rel intensity) 298 (M^+, 100), 285 (14), 218 (17), 178 (31), 143 (34), 115 (13), 90 (14); HRMS *m/z* calc. for $C_{12}H_{12}N_2BrCl$ 297.9872, found 297.9868.

2-Bromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoroaniline (4). Yield 77%. White solid, mp 97-98 °C. TLC (30% EtOAc/hexane) R_f 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, 1H, J = 1.7 Hz), 6.81 (dd, 1H, J = 11.0, 2.2 Hz), 5.78 (s, 2H), 4.17 (s, 2H), 1.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2(d, J = 244.1 Hz), 133.4(d, J = 14.1 Hz), 129.09, 129.01, 127.6, 114.7(d, J = 19.9 Hz), 108.7(d, J = 5.0 Hz), 105.7, 12.8; IR 3462, 3356, 3053, 2980, 1610, 1578, 1549, 1483, 1410 cm^{-1}; GC-MS *m/z* (rel intensity) 282 (M^+, 100), 267 (14), 226 (7), 202 (19), 187(24), 162 (40), 108 (14); HRMS *m/z* calc. for $C_{12}H_{12}N_2BrF$ 282.0168, found 282.0069.

2-Bromo-6-methoxy-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline (5). Yield 84%. Yellow liquid. TLC (30% EtOAc/hexane) R_f 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, 1H, J = 2.0 Hz), 6.51(d, 1H, J = 2.0 Hz), 5.79 (s, 2H), 4.24 (s, 2H), 3.76 (s, 3H), 1.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 134.4, 129.16, 129.11, 123.9 (d, J = 2.5 Hz), 109.7 (d, J = 4.1 Hz), 107.3, 105.36, 105.3(d, J = 3.3 Hz), 56.0 (d, J = 2.9 Hz), 12.8; IR 3468, 3371, 3055, 2928, 1612, 1574, 1497, 1462 cm^{-1}; GC-MS *m/z* (rel intensity) 294 (M^+, 100), 279 (35), 251 (26), 238 (17), 199(16), 171 (14), 159 (20), 78 (22); HRMS *m/z* calc. for $C_{13}H_{15}N_2BrO$ 294.1755, found 294.0326.

2,6-Dibromo-4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)aniline (6). Yield 63%. White solid, mp 146-147 °C. TLC (30% EtOAc/hexane) R_f 0.64; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 2H), 7.18-7.10 (m, 5H), 6.29 (d, 1H, J = 3.2 Hz), 6.03 (d, 1H, J = 3.2 Hz), 4.62 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 134.2, 133.0, 131.9, 131.6, 130.4, 128.1, 127.7, 125.9, 108.6, 107.7, 107.5, 13.2; IR 3418, 3333, 3070, 2974, 1612, 1582, 1512, 1477, 1404 cm^{-1}; GC-MS *m/z* (rel intensity) 404 (M^+, 100), 286 (24), 245 (14), 204 (9), 115(14); HRMS *m/z* calc. for $C_{17}H_{14}N_2Br_2$ 403.9524, found 403.9535.

2,6-Dichloro-4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)aniline (7). Yield 67%. White solid, mp 132-133 °C. TLC (30% EtOAc/hexane) R_f 0.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.09 (m, 5H), 7.02 (s, 2H), 6.29 (d, 1H, J = 3.2 Hz), 6.03 (d, 1H, J = 3.2 Hz), 4.62 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 134.2, 133.1, 131.9, 129.5, 128.1, 127.9, 127.7, 125.9, 119.0, 108.7, 107.5, 13.1; IR 3472, 3367, 3009, 2989, 1616, 1585, 1489, 1277, 1261 cm^{-1}; GC-MS *m/z* (rel intensity) 316 (M^+, 100), 240 (54), 178

(14), 140 (12), 124(15), 115 (21); HRMS *m/z* calc. for $C_{17}H_{14}N_2Cl_2$ 316.0534, found 316.0533.

2-Bromo-6-chloro-4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)aniline (8). Yield 82%. White solid, mp 115-116 °C. TLC (30% EtOAc/hexane) R_f 0.64; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-714 (m, 7H), 6.35 (d, 1H, *J* = 3.2 Hz), 6.09 (d, 1H, *J* = 3.2 Hz), 4.62 (s, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 134.3, 133.1, 131.9, 131.0, 128.5, 128.1, 127.7, 125.9, 118.6, 108.7, 108.2, 107.6, 107.5, 13.1; IR 3468, 3364, 3074, 2932, 1616, 1582, 1512, 1481, 1288 cm^{-1}; GC-MS *m/z* (rel intensity) 360 (M^+, 100), 284 (12), 240 (29), 204 (9), 115(14); HRMS *m/z* calc. for $C_{17}H_{14}N_2BrCl$ 360.0029,found 360.0027.

2-Bromo-6-fluoro-4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)aniline (9). Yield 82%. Pale yellow solid, mp 135-136 °C. TLC (30% EtOAc/hexane) R_f 0.72 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.04 (m, 6H), 6.72 (dd, 1H, *J* = 11.0, 2.0 Hz), 6.23 (d, 1H, *J* = 3.2 Hz), 5.98 (d, 1H, *J* = 3.2 Hz), 4.12 (s, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1 (d, *J* = 245.0 Hz), 134.3, 133.2 (d, *J* = 14.1Hz), 133.1, 131.9, 129.6 (d, *J* = 9.9 Hz), 128.1, 127.7, 127.6, 125.9, 115.05 (d, *J* = 20.7 Hz), 115.01 (d, *J* = 20.7 Hz), 108.7, 108.67, 108.62, 107.5 (d, *J* = 4.1 Hz), 13.1; IR 3468, 3371, 3074, 2920, 1628, 1589, 1574, 1493, 1173 cm^{-1}; GC-MS *m/z* (rel intensity) 344 (M^+, 100), 264 (15), 224 (72), 162 (15), 132(15), 115 (3); HRMS *m/z* calc. for $C_{17}H_{14}N_2BrF$ 344.0324, found 344.0287.

2-Bromo-6-methoxy-4-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)aniline (10). Yield 85%. White solid, mp 158-159 °C. TLC (10% EtOAc/hexane) R_f 0.24 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.08 (m, 6H), 6.96 (d, 1H, *J* = 2.3 Hz), 6.44 (d, 1H, *J* = 2.3 Hz), 6.31 (d, 1H, *J* = 3.7 Hz), 6.04 (d, 1H, *J* = 4.1 Hz), 4.24 (s, 2H), 3.65 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 134.3, 133.5, 132.1, 129.8, 128.1, 127.7, 125.8, 124.0, 110.2, 108.4, 107.3, 56.1, 13.4; IR 3472, 3387, 3070, 2924, 1651, 1574, 1497, 1489cm^{-1}; GC-MS *m/z* (rel intensity) 356 (M^+, 100), 341 (12), 262 (17), 217 (7), 156 (5), 115 (7); HRMS *m/z* calc. for $C_{18}H_{17}N_2BrO$ 356.0524, found 356.0522.

3. General procedure for the Paal-Knorr reaction of 4-(1*H*-pyrrol-1-yl)anilines with 2,5-hexanedione to obtain ((1*H*-pyrrol-1-yl)phenyl)-1*H*-pyrroles

The 4-(1*H*-pyrrol-1-yl)aniline derivative (1.0 mmol) was added to a mixture of *p*-TsOH·H_2O (0.02 equiv) and $MgSO_4$ (2–3 equiv) in toluene (1.5 mL), followed by the addition of 2,5-hexanedione or 1-phenyl-1,4-pentanedione (1.0 mmol) in toluene (1 mL). The resulting reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with EtOAc (20 mL) and poured onto a 10% aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer extracted with EtOAc (20 mL × 3) or CH_2Cl_2 (20 mL × 3). The combined organic layers were dried

over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue purified using flash column chromatography on neutral silica gel eluted with hexane for most derivatives or EtOAc/hexane (v/v = 5/95) for the pyrrole-ring substituted amino-benzene derivatives to give the corresponding bis-pyrrole products. The structures of the bis-pyrrole products, which were mostly novel compounds, were characterized using ^{1}H NMR, ^{13}C NMR and FTIR spectroscopy, GC–MS, and HRMS.

1,1'-(2,6-Dibromo-1,4-phenylene)bis(2,5-dimethyl-1*H*-pyrrole) (11). Yield 15%. Pale yellow solid, mp 195 °C; TLC (30% EtOAc/hexane) R_f 0.81; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 2H), 5.99 (s, 2H), 5.93 (s, 2H), 2.12 (s, 6H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.1, 131.8, 128.6, 127.4, 125.6, 107.1, 107.0, 106.4, 106.3, 13.0, 13.0, 12.2, 12.2; IR 3038, 2918, 1593, 1495, 1394, 1065 cm^{-1}; GC-MS *m/z* (rel intensity) 420 (M^+, 100), 247 (10), 210 (19), 167(15); HRMS *m/z* calc. for $C_{18}H_{18}N_2Br_2$ 419.9837, found 419.9838.

1,1'-(2,6-Dichloro-1,4-phenylene)bis(2,5-dimethyl-1*H*-pyrrole) (12). Yield 22%. Pale yellow solid, mp 112-113 °C. TLC (30% EtOAc/hexane) R_f 0.81; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 5.99 (s, 2H), 5.92 (s, 2H), 2.10 (s, 6H), 1.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 136.2, 134.3, 128.5, 128.1, 1279, 107.1, 106.5, 13.0, 12.0; IR 3059, 2920, 1593, 1489, 1385 cm^{-1}; GC-MS *m/z* (rel intensity) 332 (M^+, 100), 166 (23), 140 (9), 77 (4), 53 (11); HRMS *m/z* calc. for $C_{18}H_{18}N_2Cl_2$ 332.0847, found 332.0835.

1,1'-(2-Bromo-6-chloro-1,4-phenylene)bis-(2,5-dimethyl-1*H*-pyrrole) (13). Yield 13%. Pale yellow solid, mp 137-138 °C. TLC (30% EtOAc/hexane) R_f 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 2.0 Hz), 7.40 (d, 1H, J = 2.0 Hz), 6.00 (s, 2H), 5.93 (s, 2H), 2.12 (s, 6H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 140.4, 135.9, 135.7, 131.2, 128.7, 128.7, 128.6, 127.7, 125.9, 107.1, 106.9, 106.5, 106.3, 13.06, 13.03, 12.21, 12.17; IR 3043, 2920, 1589, 1501, 1439, 1396 cm^{-1}; GC-MS *m/z* (rel intensity) 376 (M^+, 100), 361 (5), 188 (20), 167 (9); HRMS *m/z* calc. for $C_{18}H_{18}N_2BrCl$ 376.0342, found 376.0329.

1,1'-(2-Bromo-6-fluoro-1,4-phenylene)bis-(2,5-dimethyl-1*H*-pyrrole) (14). Yield 63%. Pale brown solid, mp 136-137 °C. TLC (30% EtOAc/hexane) R_f 0.81; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, 1H, J = 2.0 Hz), 7.04 (dd, 1H, J = 9.0, 2.0 Hz), 5.93 (s, 2H), 5.87 (s, 2H), 2.05 (s, 6H), 1.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (d, J = 254.9 Hz), 140.8 (d, J = 9.9 Hz), 128.53 (d, J = 15.7 Hz), 128.3 (d, J = 3.3 Hz), 126.54 (d, J = 15.7 Hz), 125.9, 115.8, 115.6, 107.0, 106.6, 13.0, 12.2; IR 3067, 2922, 2854, 1605, 1556, 1495, 1377, 1302 cm^{-1}; GC-MS *m/z* (rel intensity) 360 (M^+, 100), 345 (7), 265 (9), 180 (19), 132 (5); HRMS *m/z* calc. for $C_{18}H_{18}N_2BrF$ 360.0637, found 360.0604.

1,1'-(2-Bromo-6-methoxy-1,4-phenylene)bis(2,5-dimethyl-1*H*-pyrrole) (15). Yield 88%. Pale yellow solid, mp 146-147 ºC. TLC (30% EtOAc/hexane) R_f 0.76; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 1H, *J* = 2.0 Hz), 6.84 (d, 1H, *J* = 2.0 Hz), 5.98 (s, 2H), 5.93 (s, 2H), 3.77 (s, 3H), 2.12 (s, 6H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 140.5, 128.6, 128.2, 1269, 125.8, 124.3, 111.3, 106.5, 105.8, 56.4, 12.9, 12.2; IR 3070, 2920, 1593, 1562, 1493, 1389, 1250 cm^{-1}; GC-MS *m/z* (rel intensity) 372 (M^+, 100), 357 (17), 341 (12), 277 (16), 186(20), 154(16), 77 (12); HRMS *m/z* calc. for $C_{19}H_{21}N_2BrO$ 372.0837, found 372.0837.

1-(3,5-Dibromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)-2-methyl-5-phenyl-1*H*-pyrrole (16). Yield 32%. Pale yellow solid, mp 198-199 ºC. TLC (30% EtOAc/hexane) R_f 0.81; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.24-7.26 (m, 5H), 6.36 (d, 1H, *J* = 3.4 Hz), 6.12 (d, 1H, *J* = 3.4 Hz), 5.92 (s, 2H), 2.25 (s, 3H), 1.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.2, 134.7, 133.1, 132.6, 131.9, 128.5, 128.2, 127.6, 126.7, 125.7, 110.0, 109.0, 106.8, 13.4, 12.2; IR 3070, 2924, 1585, 1477, 1377 cm^{-1}; GC-MS *m/z* (rel intensity) 482 (M^+, 100), 309 (7), 241 (20), 167 (8), 115 (5); HRMS *m/z* calc. for $C_{23}H_{20}N_2Br_2$ 481.9993, found 481.9939.

1-(3,5-Dichloro-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)-2-methyl-5-phenyl-1*H*-pyrrole (17). Yield 70%. Pale yellow solid, mp 135-136 ºC. TLC (30% EtOAc/hexane) R_f 0.76; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 7.08-7.02 (m, 5H), 6.28 (d, 1H, *J* = 3.4 Hz), 6.03 (d, 1H, *J* = 3.4 Hz), 5.84 (s, 2H), 2.16 (s, 3H), 1.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 136.1, 134.4, 133.9, 132.6, 131.2, 128.4, 128.1, 127.9, 127.8, 126.4, 109.7, 108.7, 106.5, 13.3, 11.9; IR 3070, 2920, 1597, 1489, 1385 cm^{-1}; GC-MS *m/z* (rel intensity) 394 (M^+, 100), 197 (20), 167 (6), 115 (9), 77 (5); HRMS *m/z* calc. for $C_{23}H_{20}N_2Cl_2$ 394.1004, found 394.1005.

1-(3-Bromo-5-chloro-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)-2-methyl-5-phenyl-1*H*-pyrrole (18). Yield 25%. Pale yellow solid, mp 169-170 ºC. TLC (30% EtOAc/hexane) R_f 0.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 2.0 Hz), 7.24 (d, 1H, *J* = 2.0 Hz), 7.16-6.99 (m, 5H), 6.32 (d, 1H, *J* = 3.4 Hz), 6.08 (d, 1H, *J* = 3.4 Hz), 5.93 (s, 2H), 2.21 (s, 3H), 1.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 135.8, 134.4, 132.6, 131.4, 131.2, 129.0, 128.1, 127.9, 127.5, 126.4, 125.8, 109.6, 108.7, 106.4, 13.3, 12.0; IR 3070, 2916, 1589, 1481, 1377, 1300 cm^{-1}; GC-MS *m/z* (rel intensity) 438 (M^+, 100), 307 (6), 265 (6), 219 (25), 167(11), 115 (9); HRMS *m/z* calc. for $C_{23}H_{20}N_2BrCl$ 438.0498, found 438.0476.

1-(3-Bromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole (19). Yield 67%. white solid, mp 117-118 ºC. TLC (30% EtOAc/hexane) R_f 0.74; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.28 (t, 1H, *J* = 1.7 Hz), 7.13-7.10 (m, 3H), 6.99 (dd, 2H, *J* = 8.2, 1.6 Hz), 6.91 (dd, 1H, *J* = 9.0, 2.2 Hz) 6.30 (d, 1H, *J* = 3.4 Hz), 6.06 (d, 1H, *J* = 3.4 Hz), 5.91 (s, 2H), 2.19 (s, 3H), 1.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (d, *J* = 255.7 Hz), 141.3 (d, *J* = 9.9 Hz), 134.4, 132.7, 131.2, 128.5 (d, *J* = 3.3 Hz), 128.3, 128.1, 127.8, 126.4, 126.2 (d, *J* = 15.7 Hz), 125.7, 116.1 (d, *J* = 22.3 Hz), 109.7 (d, *J* = 2.5 Hz), 108.7 (d, *J* = 3.3 Hz), 106.6 (d, *J* = 9.9 Hz), 13.3, 12.0; IR 3076, 2922, 1607, 1556, 1499, 1429, 1377, 1308, 1271 cm^{-1}; GC-MS *m/z* (rel intensity) 422 (M^+, 100), 327 (7), 248 (9), 211 (22), 185(4), 115 (8); HRMS *m/z* calc. for $C_{23}H_{20}N_2BrF$ 422.0794, found 422.0792.

1-(3-Bromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole (20). Yield 77%. White solid, mp 119-120 °C. TLC (10% EtOAc/hexane) R_f 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.08 (m, 6H), 6.61 (d, 1H, *J* = 1.8 Hz), 6.39 (d, 1H, *J* = 3.2 Hz), 6.13 (d, 1H, *J* = 2.7 Hz), 5.96 (s, 2H), 3.51 (s, 3H), 2.29 (s, 3H), 1.95(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 140.9, 134.4, 133.2, 131.3, 128.2, 128.1, 127.9, 126.4, 126.3, 125.7, 124.2, 112.1, 109.3, 108.4, 105.8, 56.4, 13.5, 12.2; IR 3070, 2924, 1597, 1566, 1497, 1381, 1234 cm^{-1}; GC-MS *m/z* (rel intensity) 434 (M^+, 100), 403 (6), 339 (6), 217 (15), 202 (4), 115 (4); HRMS *m/z* calc. for $C_{24}H_{23}N_2BrO$ 434.0994, found 434.1011.

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