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Catalyst-free four-component protocol for the synthesis of substituted pyrroles under reusable reaction media

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ABSTRACT

An efficient four-component protocol is described for the synthesis of diversely functionalized pyrroles under catalyst-free condition by using ionic liquid as a reaction media. The developed method is mild, high yielding, and amenable for a variety of amines as well as aldehydes. Moreover the procedure is of environmentally benign nature in which ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 is used as a reusable and efficient reaction medium without using any additional catalyst or promoter.

Pyrrole is an important core unit found in many natural products,[1] pharmaceutically active compounds, (Fig. 1) and electrical conducting materials.[2] In addition to this, pyrrole derivatives are known to possess a wide range of biological activities such as antitumor, anti-inflammatory, antibacterial, antioxidant, and antifungal.[3] Due to such prominence of pyrroles, numerous methods[4–10] have been reported for the synthesis of these molecules where the most commonly used approaches include Hantzsch[4], Knorr[5] and Paal–Knorr[6] syntheses. In an alternate method, the synthesis of pyrrole has been accomplished by the reaction of bromonitrostyrenes with enamines.[11] Recently a four-component reaction of amines, aldehyde, diketone, and nitroalkane is reported to give functionalized pyrroles[12a,b] by using $FeCl_3$,[12a] and $NiCl_2{\cdot}6H_2O$.[12b] However this method possesses certain drawbacks such as the use of toxic metal catalysts and harsh reaction conditions. Moreover these methods use non-ecofriendly organic solvents and give a moderate yield of product even after a longer reaction time. In this regard, the development of an efficient method for the synthesis of pyrrole derivatives under mild reaction condition is highly desirable.

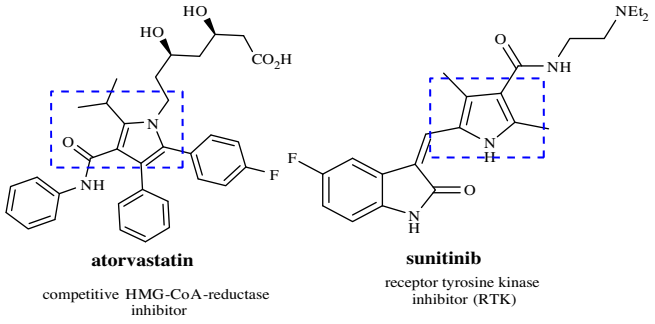

Figure 1. Representative examples of biologically active pyrrole derivatives.

Nowadays, sustainable processes are highly in demand in the chemical industry.[13] The 'process efficiency' concept is not only related to a high chemical yield, but also to minimize the use of large amounts of harmful organic reagents, solvents, catalyst, and undesired chemical waste.[14] In this context, ionic liquids have been emerging as a mild and environmentally benign reaction medium in modern chemical synthesis.[15] Also ionic liquid promotes the different organic transformations without the use of any additional catalyst or solvent.[16]

In a recent article, Jana et al. found that, β-enaminone and β-nitrostyrene are key intermediates in the pyrrole synthesis[12b] and our literature survey revealed that the synthesis of these key intermediates can be achieved in ionic liquid.[17a,b] Keeping this in mind, we envisioned the catalyst-free four-component reaction of amines, aldehyde, diketone, and nitroalkane to give functionalized pyrroles by using ionic liquid as a reaction medium (Scheme 1). To the best of our knowledge there is no report concerning the catalyst-free four-component synthesis of pyrroles. Hence, as a part of our[16] ongoing interest in the application of ionic liquids for the synthesis of biologically active molecules, herein we wish

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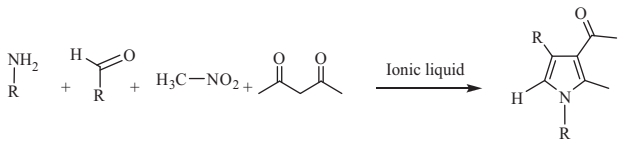


Scheme 1. Envisioned reactions of amines, aldehyde, diketone, and nitroalkane for the synthesis of substituted pyrroles under catalyst-free condition by using ionic liquid.

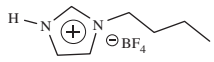
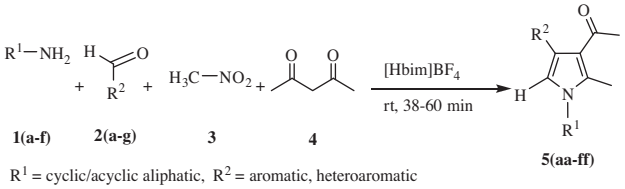


Figure 2. Chemical structure of 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 ionic liquid.



Scheme 2. Synthesis of substituted pyrroles under catalyst-free condition by using [Hbim]BF_4 as a reaction medium.

to report the catalyst-free, mild, and high yielding four component protocol for the synthesis of diversely functionalized pyrroles by using ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 (Fig. 2) as a reusable reaction medium.

As a model reaction we first attempted the reaction of cyclopropylamine **1a** (1.2 mmol), benzaldehyde **2a** (1 mmol), acetylacetone 4 (1 mmol), and nitromethane **3** (1 mmol) in 5 mL ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 (Scheme 2) and progress of the reaction was monitored continuously by TLC. The reaction proceeded smoothly within 52 min at room temperature to give substituted pyrrole **5aa** which was confirmed by analyzing spectral data (Table 2, entry 1). The formation of the desired product was also confirmed by comparison with the spectral data obtained for a sample prepared by one of the available literature procedures.[12a] The above observations reveal that the substituted pyrrole can be obtained by four-component reaction of amines, aldehyde, diketone, and nitroalkane in ionic liquid under catalyst-free condition.

These encouraging observations promoted us to screen the different imidazole based ionic liquids to study the model reaction in detail. We have studied model reaction in different ionic liquids such as, 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4, 1-butyl-3-methylimidazolium hexafluoro phosphate [bmim]PF_6, and 1-ethyl-3-methylimidazolium tetrafluoroborate [emim]BF_4. After this extensive screening, we found ionic liquid [Hbim]BF_4 as a most suitable reaction medium for model reaction in terms of reaction time and isolated yield (Table 1, entry 1). We found that the reaction worked very well in ionic liquid [Hbim]BF_4 without using additional catalyst and gave very high yields of product within a shorter reaction time at rt as compared to the previous methods.[12a,b] The exact reason for this is not well understood, but we assume that, due to the distinctive acidity and polarity associated with [Hbim]BF_4, it plays a dual role as catalyst as well as solvent and hence resulted in a higher yield of product. As a part of study, we have also performed control reaction under a neat reaction condition; however the desired product was formed in very trace amount even after strengthening the reaction time up to 24 h (Table 1, entry 6). On the basis of above study we have chosen the use

Table 1
Screening of reaction media[a]

Entry	Reaction media	Time (min)	Yield[b](%)
1	[Hbim]BF_4	52	85
2	[Hbim]BF_4	90	86
3	[bmim]BF_4	90	78
4	[bmim]PF_6	90	71
5	[emim]BF_4	90	58
6	-	24 h	trace[c]

[a]Reaction condition: cyclopropylamine **1a** (1.2 mmol), benzaldehyde **2a** (1 mmol), acetylacetone **4** (1 mmol), and nitromethane **3** (1 mmol) in 5 mL ionic liquid.
[b]Isolated yield.
[c]Under neat reaction condition.

of 5 mL [Hbim]BF_4 as an optimized reaction condition for the synthesis of substituted pyrrole **5aa** by catalyst-free four-component reaction of cyclopropylamine **1a**, benzaldehyde **2a**, acetylacetone **4**, and nitromethane **3** at rt under reusable reaction media (Table 1, entry 1).

Further, for the general validity of the reaction, the optimized condition[18,19] was tested on several structurally varied amines as well as aldehydes and the results are summarized in Table 2. The reaction of benzylamine (entries 12–14) and 2-phenylethylamine (entries 17–23) underwent smoothly in the standard reaction condition to furnish the desired product in a high yield. It is worthy to mention that the procedure is also applicable for cyclicamines like cyclopropylamine and cyclohexylamine (entries 1–7 and 8–11, respectively) and alkynylamines like propargylamine (entries 24–29) which were totally unexplored in the pyrrole synthesis. The efficiency of the reaction was further strengthened by the participation of heterocyclic aldehyde in this four-component reaction (entries 5, 10, 21, 28). For example the reaction of cyclopropylamine **1a** with furfural **2e** also proceeded same way and afforded corresponding product **5ae** in good yield (entry 5). Other diversely functionalized aldehydes also participated effectively in the reaction under optimized condition (Table 2). In our protocol, other different functional groups such as halides, hydroxyl, methoxy, acetyl, nitro, and alkynyl remained unaffected and the exclusive formation of pyrrole derivative was observed. It is worthy to mention that, in the present study the scope of the developed method was tested on new substrates and hence all obtained substituted pyrrole derivatives are new compounds.

Our next approach was to study the scope of reusability of [Hbim]BF_4 for this four-component reaction. Hence, after completion of the reaction, the reaction mixture was isolated from [Hbim]BF_4 by simply extracting with ether (3×15 mL). Then the [Hbim]BF_4 was dried under vacuum and used for subsequent reactions. We reused [Hbim]BF_4 up to three cycles for this four component reaction and did not find any substantial loss in the catalytic activity of [Hbim]BF_4 (first cycle: Table 2, entry 7, second cycle: Table 2, entry 19, third cycle: Table 2, entry 24).

The tentative mechanistic pathway based on one of the literature reports[12a] is proposed for the catalyst-free synthesis of functionalized pyrroles by using ionic liquid as a reaction medium as shown in Scheme 3. We reasoned that the reaction proceeded to form β-enaminone by the condensation of acetylacetone with amine.[17a] This reactive β-enaminone attacked on in situ generated β-nitro styrene[17b] and forms five membered cyclic intermediate **A**. Finally the cyclic intermediate undergoes aromatization by the elimination of water molecule with the aid of ionic liquid and gives substituted pyrrole derivative.

Table 2
Synthesis of substituted pyrroles[a] in $[Hbim]BF_4$

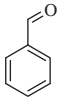
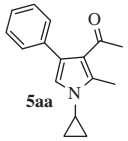
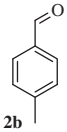
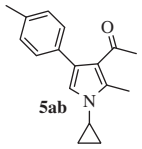
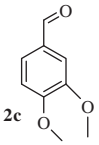
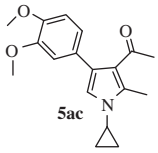
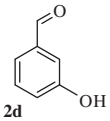
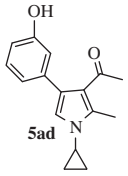
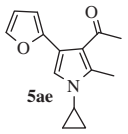
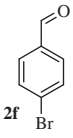
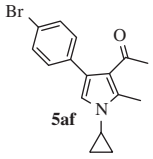
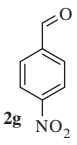
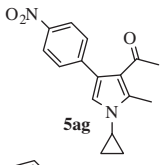
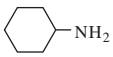
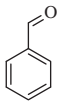
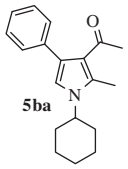
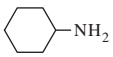
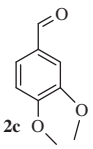
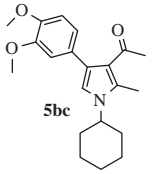
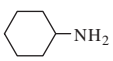
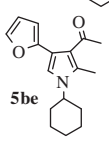
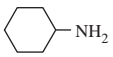
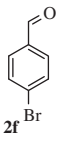
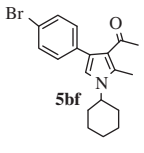
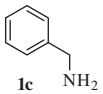
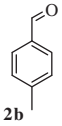
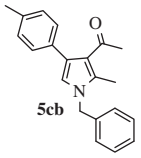
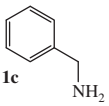
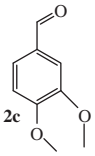
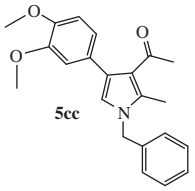
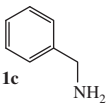
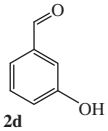
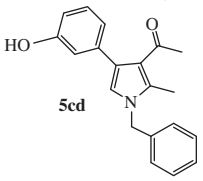
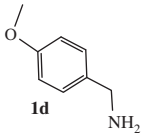
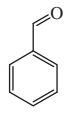
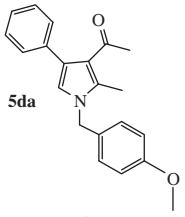
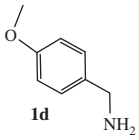
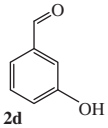
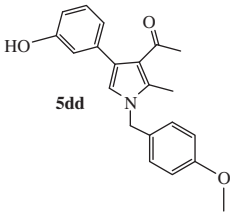
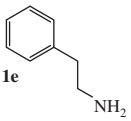
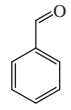
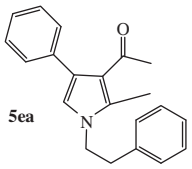
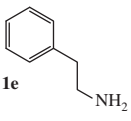
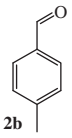
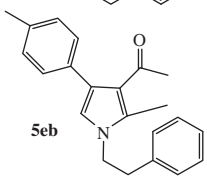
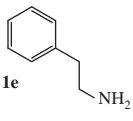
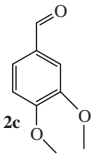
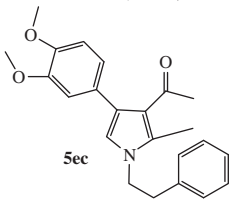
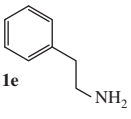
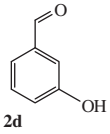
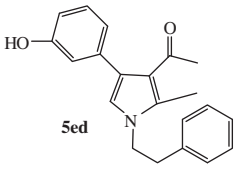
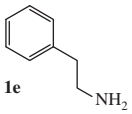
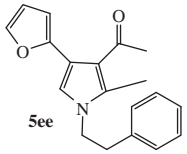
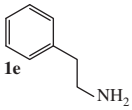
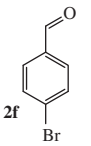
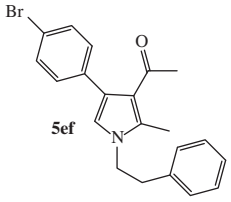
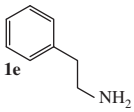
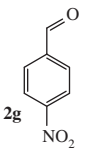
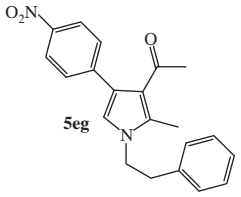
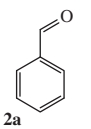
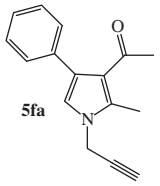
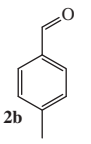
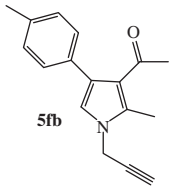
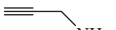
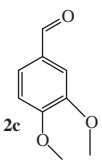
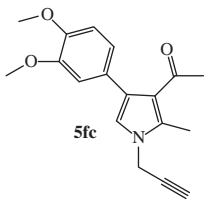
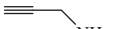
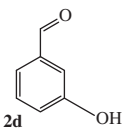
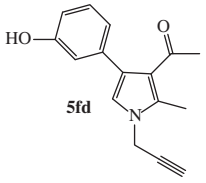
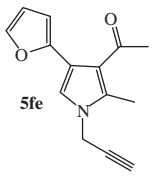
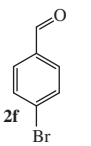
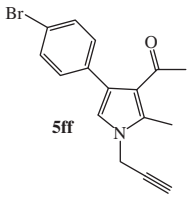
Entry	Amine (R^1)	Aldehyde (R^2)	Time (min)	Yield[b] (%)	Product
1	 **1a**	 **2a**	52	85	 **5aa**
2	 **1a**	 **2b**	50	87	 **5ab**
3	 **1a**	 **2c**	52	87	 **5ac**
4	 **1a**	 **2d**	50	85	 **5ad**
5	 **1a**	 **2e**	54	88	 **5ae**
6	 **1a**	 **2f**	60	70	 **5af**
7	 **1a**	 **2g**	60	75	 **5ag**
8	 **1b**	 **2a**	54	82	 **5ba**
9	 **1b**	 **2c**	55	83	 **5bc**
10	 **1b**	 **2e**	56	89	 **5be**
11	 **1b**	 **2f**	60	70	 **5bf**

Table 2 (*continued*)

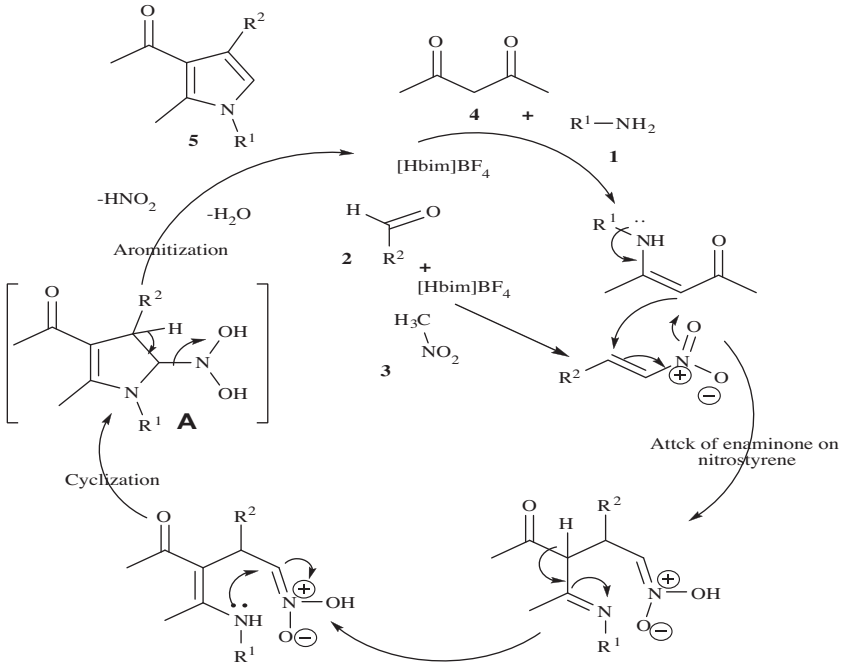
Entry	Amine (R^1)	Aldehyde (R^2)	Time (min)	Yield[b] (%)	Product
12	 **1c**	 **2b**	40	90	 **5cb**
13	 **1c**	 **2c**	40	86	 **5cc**
14	 **1c**	 **2d**	38	89	 **5cd**
15	 **1d**	 **2a**	45	93	 **5da**
16	 **1d**	 **2d**	38	90	 **5dd**
17	 **1e**	 **2a**	45	93	 **5ea**
18	 **1e**	 **2b**	40	90	 **5eb**
19	 **1e**	 **2c**	40	88	 **5ec**
20	 **1e**	 **2d**	38	92	 **5ed**

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine (R^1)	Aldehyde (R^2)	Time (min)	Yield[b] (%)	Product
21	 **1e**	 **2e**	40	87	 **5ee**
22	 **1e**	 **2f**	55	75	 **5ef**
23	 **1e**	 **2g**	55	78	 **5eg**
24	**1f**	 **2a**	50	88	 **5fa**
25	**1f**	 **2b**	48	90	 **5fb**
26	 **1f**	 **2c**	40	89	 **5fc**
27	 **1f**	 **2d**	48	94	 **5fd**
28	**1f**	 **2e**	40	89	 **5fe**
29	**1f**	 **2f**	55	77	 **5ff**

[a] All products exhibited physical and spectral (NMR, Mass, and IR) properties in accordance with the assigned structure.
[b] Isolated Yield.



Scheme 3. Plausible mechanistic pathway for the formation of substituted pyrrole in the presence of $[Hbim]BF_4$.

In conclusion, we have demonstrated an operationally simple, efficient, and catalyst-free method for the synthesis of diversely functionalized pyrrole derivatives using ionic liquid $[Hbim]BF_4$ as a reusable reaction medium. Moreover the method is applicable to variety of amines as well as aldehydes and the yields are high. This method ought to be of great value as a mild, rapid, and general procedure for the synthesis of highly substituted pyrroles. Further studies for the scope and limitations of this methodology are currently ongoing in our laboratory and results will be published elsewhere in due course.

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Supplementary data

Supplementary data (spectral data for synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.098.

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18. *General procedure:* A mixture of amine (1.2 mmol), acetylacetone (1 mmol) in 5 mL ionic liquid [Hbim]BF_4 was stirred for 10 min at room temperature then the aldehyde (1 mmol) and nitromethane (1 mL) were added and the mixture was stirred at rt for a stipulated time (see Table 1). The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine solution, and dried over Na_2SO_4. Na_2SO_4 was filtered off and the solvent was removed under vacuum. The residue obtained was then purified by silica gel column chromatography (100–200 mesh) using ethyl acetate/hexane (5:95 to 20:80) as eluent to get corresponding products. All the obtained products were characterized by ^{1}H NMR, ^{13}C NMR, Mass, and IR spectral data.
19. *Spectral data for synthesized compounds:*
1-(1-cyclopropyl-4-(3,4-dimethoxyphenyl)-2-methyl-1H-pyrrol-3-yl) ethanone (**5ac,** Table 2, entry 3): White solid, mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90–6.79 (m, 3H), 6.49 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.20–3.11 (m, 1H), 2.58 (s, 3H), 2.02 (s, 3H), 1.09–1.01 (m, 2H), 1.00–0.92 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 148.3, 147.8, 137.0, 128.9, 124.5, 121.7, 121.3, 119.1, 112.6, 110.8, 55.7, 55.6, 30.6, 27.9, 11.9, 6.5 ppm; IR(KBr): ν = 3424, 1644, 1508, 1456, 1417, 1239, 1171, 1137, 1016, 852, 814, 760 cm^{-1}; MS-ESI: m/z = 300 [M+1]$^+$. *1-(1-cyclopropyl-4-(furan-2-yl)-2-methyl-1H-pyrrol-3-yl) ethanone* (**5ae**, Table 2, entry 5): White solid, mp 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 1.13 Hz, 1H), 6.69 (s, 1H), 6.42 (dd, J = 2.83, 1.13 Hz, 1H), 6.34 (d, J = 2.83 Hz, 1H), 3.19–3.10 (m, 1H), 2.59 (s, 3H), 2.14 (s, 3H), 1.10–1.01 (m, 2H), 1.00–0.91 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 149.0, 141.4, 137.7, 121.0, 120.7, 113.7, 110.9, 107.5, 29.6, 28.1, 12.1, 6.6 ppm; IR(KBr): ν = 3119, 1652, 1574, 1439, 1165, 985, 859, 783, 767 cm^{-1}; MS-ESI: m/z = 230 [M+1]$^+$. *1-(4-(4-Bromophenyl)-1-cyclopropyl-2-methyl-1H-pyrrol-3-yl) ethanone* (**5af**, Table 2, entry 6): Red viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.49 Hz, 2H), 7.17 (d, J = 8.49 Hz, 2H), 6.51 (s, 1H), 3.20–3.12 (m, 1H), 2.56 (s, 3H), 2.02 (s, 3H), 1.10–0.90 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 137.5, 135.1, 131.7, 131.0, 130.6, 127.5, 123.5, 119.5, 30.7, 28.0, 12.0, 6.6 ppm; IR(KBr): ν = 3354, 3014, 1648, 1553, 1511, 1417, 1383, 1222, 1071, 1010, 831, 762 cm^{-1}; MS-ESI: m/z = 318 [M]$^+$, 320 [M+2]$^+$. *1-(1-Cyclohexyl-4-(furan-2-yl)-2-methyl-1H-pyrrol-3-yl) ethanone* (**5be**, Table 2, entry 10): Orange Yellow viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 1.97 Hz, 1H), 6.76 (s, 1H), 6.42 (dd, J = 2.96, 1.97 Hz, 1H), 6.32 (d, J = 2.96 Hz, 1H), 3.91–3.84 (m, 1H), 2.51 (s, 3H), 2.13 (s, 3H), 2.02–1.16 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 149.4, 141.4, 134.7, 120.6, 117.1, 114.4, 110.9, 107.4, 55.0, 33.8, 29.7, 25.7, 25.2, 11.3 ppm; IR(KBr): ν = 3137, 1655, 1530, 1187, 1059, 978, 843, 762, 727 cm^{-1}; MS-ESI: m/z = 272 [M+1]$^+$. *1-(4-(4-Bromophenyl)-1-cyclohexyl-2-methyl-1H-pyrrol-3-yl) ethanone* (**5bf**, Table 2, entry 11): Red viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 8.49 Hz, 2H), 7.14 (d, J = 8.49 Hz, 2H), 6.53 (s, 1H), 3.92–3.76 (m, 1H), 2.42 (s, 3H), 1.96 (s, 3H), 1.88–1.12 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 135.8, 132.9, 130.1, 125.2, 123.3, 122.1, 107.9, 107.4, 59.7, 33.7, 29.1, 25.9, 25.3, 11.8 ppm; IR(KBr): ν = 3276, 2932, 2856, 1648, 1605, 1556, 1413, 1304, 1196, 1010, 830, 756 cm^{-1}; MS-ESI: m/z = 360 [M]$^+$, 362 [M+2]$^+$. *1-(1-Benzyl-2-methyl-4-p-tolyl-1H-pyrrol-3-yl) ethanone* (**5cb**, Table 2, entry 12): White solid, mp 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.02 (m, 9H), 6.58 (s, 1H), 4.97 (s, 2H), 2.35 (s, 3H), 2.26 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 135.4, 133.7, 132.5, 131.5, 127.1, 126.9, 126.8, 125.6, 124.8, 123.2, 119.7, 118.5, 47.8, 28.9, 18.9, 9.5 ppm; IR(KBr): ν = 3420, 2920, 1640, 1507, 1449, 416, 1352, 1201, 1177, 943, 822, 734 cm^{-1}; MS-ESI: m/z = 326 [M+Na]$^+$. *1-(1-Benzyl-4-(3-hydroxyphenyl)-2-methyl-1H-pyrrol-3-yl) ethanone* (**5cd**, Table 2, entry 14): White solid, mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.18 (m, 3H), 7.09–7.03 (m, 3H), 6.74–6.67 (m, 3H), 6.47 (s, 1H), 4.98 (s, 2H), 2.36 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 156.2, 137.2, 136.2, 135.6, 129.4, 128.8, 127.8, 126.6, 125.9, 121.7, 120.7, 120.2, 116.3, 114.0, 50.2, 30.6, 11.5 ppm; IR(KBr): ν = 3152, 1621, 1592, 1450, 1415, 1231, 874, 774, 725, 704 cm^{-1}; MS-ESI: m/z = 306 [M+1]$^+$. *1-(4-(3,4-Dimethoxyphenyl)-2-methyl-1-phenethyl-1H-pyrrol-3-yl) ethanone* (**5ec**, Table 2, entry 19): White solid, mp 107–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.24 (m, 3H), 7.14–7.09 (m, 2H), 6.88–6.78 (m, 3H), 6.38 (s, 1H), 4.06 (t, J = 7.55 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.01 (t, J = 7.55 Hz, 2H), 2.40 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 148.3, 147.8, 137.5, 134.4, 128.9, 128.5, 128.5, 128.2, 126.7, 125.3, 121.3, 119.1, 112.6, 110.8, 55.6, 55.6, 47.8, 37.3, 30.7, 11.2 ppm; IR(KBr): ν = 3422, 2937, 1641, 1508, 1413, 1224, 1174, 1131, 1025, 756, 703 cm^{-1}; MS-ESI: m/z = 364 [M+1]$^+$. *1-(4-(3-Hydroxyphenyl)-2-methyl-1-phenethyl-1H-pyrrol-3-yl) ethanone* (**5ed**, Table 2, entry 20): White solid, mp 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.20 (m, 3H), 7.15–7.08 (m, 3H), 6.76–6.69 (m, 3H), 6.43 (s, 1H), 4.06 (t, J = 6.65 Hz, 2H), 3.00 (t, J = 6.65 Hz, 2H), 2.31 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 156.4, 138.4, 137.6, 135.9, 132.4, 128.8, 127.9, 126.8, 123.9, 120.6, 117.1, 116.4, 109.4, 109.1, 50.2, 37.6, 28.9, 11.4 ppm; IR(KBr): ν = 3186, 1622, 1598, 1508, 1450, 1419, 1363, 1237, 1165, 876, 778, 749,707 cm^{-1}; MS-ESI: m/z = 320 [M+1]$^+$.
1-(4-(Furan-2-yl)-2-methyl-1-phenethyl-1H-pyrrol-3-yl) ethanone (**5ee**, Table 2, entry 21): White solid, mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 2.00 Hz, 1H), 7.27–7.17 (m, 3H), 7.04 (d, J = 7.99 Hz, 2H), 6.56 (s, 1H), 6.39 (dd, J = 2.99, 2.00 Hz, 1H), 6.32 (d, J = 2.99 Hz, 1H), 3.97 (t, J = 6.99 Hz, 2H), 2.93 (t, J = 6.99 Hz, 2H), 2.30 (s, 3H), 2.12 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 148.9, 141.2, 137.2, 135.0, 128.5, 128.4, 126.7, 120.7, 120.4, 114.4, 110.8, 107.5, 47.8, 37.2, 29.6, 11.2 ppm; IR(KBr): ν = 3053, 1654, 1448, 1412, 1018, 996, 812, 793, 764 cm^{-1}; MS-ESI: m/z = 294 [M+1]$^+$. *1-(4-(4-Bromophenyl)-2-methyl-1-phenethyl-1H-pyrrol-3-yl) ethanone* (**5ef**, Table 2, entry 22): Red viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, J = 8.30 Hz, 2H), 7.30–7.24 (m, 3H), 7.15–7.11 (m, 2H), 7.08 (d, J = 8.30 Hz, 2H), 6.37 (s, 1H), 4.04 (t, J = 7.55 Hz, 2H), 2.99 (t, J = 7.55 Hz, 2H), 2.35 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 137.3, 135.1, 134.9, 131.7, 131.0, 130.6, 128.5, 127.5, 126.8, 124.2, 120.4, 119.4, 47.9, 37.2, 30.8, 11.2 ppm; IR(KBr): ν = 3355, 2925, 1646, 1552, 1507, 1417, 1382, 1176, 1010, 831, 754, 701 cm^{-1}; MS-ESI: m/z = 382 [M]$^+$, 384 [M+2]$^+$. *1-(2-Methyl-4-phenyl-1-(prop-2-ynyl)-1H-pyrrol-3-yl) ethanone* (**5fa**, Table 2, entry 24): White solid, mp 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.30 (m, 5H), 6.68 (s, 1H), 4.65 (d, J = 3.02 Hz, 2H), 2.58 (s, 3H), 2.48 (t, J = 3.02 Hz, 1H), 2.04 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 136.4, 134.7, 130.0, 129.2, 128.9, 127.8, 119.1, 119.0, 78.3, 74.2, 36.1, 21.1, 11.3 ppm; IR(KBr): ν = 3291, 3116, 1644, 1507, 1413, 1118, 943, 768, 703, 670, 630 cm^{-1}; MS-ESI: m/z = 238 [M+1]$^+$. *1-(4-(Furan-2-yl)-2-methyl-1-(prop-2-ynyl)-1H-pyrrol-3-yl) ethanone* (**5fe**, Table 2, entry 28): Orange Yellow viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, J = 2.00 Hz, 1H), 6.81 (s, 1H), 6.42 (dd, J = 2.99, 2.00 Hz, 1H), 6.36 (d, J = 2.99 Hz, 1H), 4.58 (d, J = 2.99 Hz, 2H), 2.51 (s, 3H), 2.46 (t, J = 2.99 Hz, 1H), 2.14 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 148.4, 141.3, 139.9, 120.1, 114.4, 110.8, 110.4, 107.5, 76.5, 74.3, 35.9, 29.5, 11.1 ppm; IR(KBr): ν = 3182, 1652, 1452, 1397, 1132, 1082, 987, 889, 812, 732 cm^{-1}; MS-ESI: m/z = 228 [M+1]$^+$. *1-(4-(4-Bromophenyl)-2-methyl-1-(prop-2-ynyl)-1H-pyrrol-3-yl) ethanone* (**5ff**, Table 2, entry 29): Red viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 8.99 Hz, 2H), 7.18 (d, J = 8.99 Hz, 2H), 6.63 (s, 1H), 4.61 (d, J = 2.99 Hz, 2H), 2.52 (s, 3H), 2.45 (t, J = 2.99 Hz, 1H), 2.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 134.5, 131.2, 130.7, 130.3, 127.3, 123.9, 120.1, 119.0, 76.6, 74.2, 35.7, 30.4, 10.8 ppm; IR(KBr): ν = 3292, 2923, 1648, 1552, 1513, 1415, 1383, 1189, 1136, 1010, 831, 763 cm^{-1}; MS-ESI: m/z = 316 [M]$^+$, 318 [M+2]$^+$.