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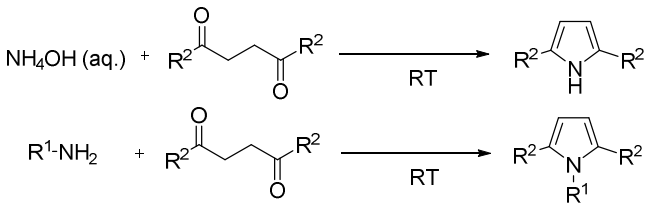
A catalyst and solvent-free room temperature synthesis of pyrroles is described.




$R^1$ = alkyl, benzyl, Ph, Ph($NH_2$), alkyl-$NH_2$
$R^2$ = methyl, phenyl

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# The Paal-Knorr reaction revisited. A catalyst and solvent-free synthesis of underivatized and N-substituted pyrroles

**Hyejin Cho,[a] Richard Madden, [a] Bilal Nisanci [a,b] and Béla Török [a],***

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A new, modified synthesis of pyrroles is described. The reaction of 2,5-hexandione with a variety of amines yielded the expected pyrrole analogues in excellent yields. The reactions were carried out under the ultimate green conditions excluding both catalyst and solvent applying simple stirring at room temperature. The variety of amines include aqueous ammonium hydroxide for the synthesis of pyrroles with free a NH group, and benzylamines, anilines and phenylene-diamines for the synthesis of several N-derivatized pyrroles. The reaction also occurs efficiently with a variety of 1,4-diketones, although the reaction rates and yields are lower for the diketones that do not possess terminal methyl group(s).





## Introduction

Heterocyclic compounds possess a wide range of biological properties such as antibacterial, antiviral, anti-inflammatory, antitumor and antioxidant activities.[1,2] Among heterocycles, the pyrrole core has always been one of the most prominent, as it is a useful intermediate in the synthesis of natural products, as well as in medicinal chemistry. Polymerized derivatives of pyrroles[3] are also widely used in materials science indicating the widespread application possibilities.

Due to the broad interest in pyrroles, the synthesis of these compounds has always been among the most important research areas in synthetic chemistry, resulting in the development of several classic named reactions. The classic methods for the synthesis of pyrroles are as follows: (i) the Hantzsch reaction,[4] which provides pyrroles from a reaction of α-halo ketones with β-ketoesters and ammonia (or primary amines); (ii) the Knorr reaction,[5] which assembles pyrroles by the reaction between α-aminoketones derived from α-haloketones and ammonia, and β-ketoesters; (iii) the Paal-Knorr reaction,[6] one of the most common approaches in which γ-diketones are converted to pyrroles from the reaction with primary amines (or ammonia) in the presence of various promoting agents.[7] Several methods, partially related to the previously mentioned general processes, were also reported for the synthesis of specific pyrroles, often as a part of a larger ring system.[8]

The Paal-Knorr synthesis has been frequently applied in the synthesis of pyrroles. In their original method, Paal[9] and Knorr[10] independently, used a weak mineral acid catalyst. Since the reaction occurs *via* the elimination of two moles of water the application of an acid catalyst appears mechanistically well-founded. The emergence of green chemistry, coupled with the continuous need for new pyrroles, resulted in extended development in the modernization of time-honored synthetic techniques, such as the Paal-Knorr reaction

Several catalysts, including green alternatives, such as solid acids, water soluble acids etc., have been applied for the synthesis of a variety of pyrroles. These catalysts include glutathione bearing nanoferrites,[11] copper iodide on activated carbon (CuI/C),[12] polystyrenesulfonate,[13] and many others as reviewed earlier.[14]

Independent of the catalysts, the presence of harmful solvents or harsh reaction conditions, the waste of energy and long and high temperature heating also presented problems. To overcome these issues, the development of more time, solvent and energy efficient procedures initiated the use of rapid and environmentally acceptable alternatives, such as microwave-assisted organic synthesis (MAOS), in favour of the classic methods that have been emphasized for the synthesis of pyrroles.[15] The use of microwave heating, environmentally benign solvents or solvent-free conditions have been introduced to avoid harmful or difficult to recycle organic solvents or severe reaction conditions (high temperatures, strong liquid acid catalysts etc.).[16,17,18] Gas phase reactions of ammonia with diketones were also investigated.[19]

Our earlier investigations resulted in the development of several green methods for the synthesis of pyrroles, indoles, and carbazoles among other heterocycles using solvent-free reaction conditions. These processes were catalyzed by an environmentally benign, microwave-active solid-acid (K-10 montmorillonite).[20,21,22] While our syntheses provided the product pyrrole derivatives in high yield, our recent data obtained in the reaction of a 1,4-diketone and amines casted doubt on the necessity of a catalyst in the Paal-Knorr reaction. In order to substantiate this observation and develop the ultimate green Paal-Knorr reaction, a detailed investigation was carried out on the subject. Herein, we report the first catalyst and solvent-

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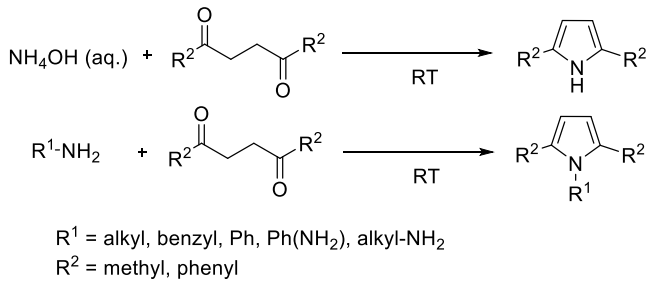
free synthesis of pyrroles at room temperature, a truly environmentally benign version of the classic Paal-Knorr pyrrole synthesis (Scheme 1).

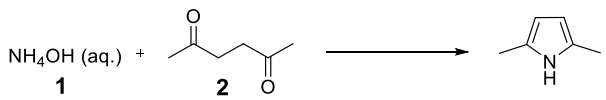



**Scheme 1** Paal-Knorr cyclization of 1,4-diones with aqueous ammonium hydroxide and primary amines

## Results and discussion

During our recent investigations, it was observed that a 1,4-diketone formed pyrrole while reacted with aqueous $NH_4OH$. This phenomenon prompted us to investigate the reaction in detail. Hexan-2,5-dione was selected as the diketone for these investigations due to our previous success with this reactant.[19-21] As a source of active $NH_2$ group, a commercially available, inexpensive aqueous ammonium hydroxide, with 28-30% $NH_3$ content, was selected. If successful, this reaction would provide pyrrole underivatized on its N-atom. While in the first attempts the reaction appeared to occur readily, a series of optimization tests were carried out to establish the conditions that result in the best performance (Table 1).

**Table 1.** Reaction of hexan-2,5-dione with aqueous $NH_4OH$




| Entry | **1**/**2** ratio[a] | activation[b] | T (˚C) | Time (h) | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | 1 | MW | 80 | 0.25 | 84 |
| 2 | 1 | US | RT | 1 | 68 |
| 3 | 2.5 | MW | 40 | 0.25 | 9 |
| 4 | 2.5 | MW | 60 | 0.25 | 30 |
| 5 | 2.5 | MW | 80 | 0.25 | 88 |
| 6 | 2.5 | - | RT | 6 | 30 |
| 7 | 2.5 | - | RT | 120 | 100 |
| 8 | 10 | - | RT | 0.5 | 60 |
| 9 | 10 | - | RT | 1 | 82 |
| 10 | 10 | - | RT | 2 | 89 |
| 11 | 10 | - | RT | 3 | 100 |

[a] 28-30% $NH_4OH$, active $NH_3$ content was taken into account in calculating reactant ratios
[b] MW-microwave activation, US-ultrasonic activation
[c] GC yields

As depicted in Table 1, the reaction proceeded efficiently under a broad range of conditions. First, two activation methods, microwave irradiation and ultrasounds, known to generate high yields in reduced times, were investigated. A 1 hour ultrasonic irradiation yielded only 68% product (Table 1, entry 2). The microwave-assisted processes performed much better, yielding up to 88% product, although requiring elevated temperatures for fast completion (Table 1, entries 1, 3-5). As the greenest possible alternative, the reaction was carried out at ambient temperature as well, without the use of any activation. The data show that while the reaction proceeds comparatively slowly (30% yield in 6 h, Table 1, entry 6) it can reach quantitative conversion without significant byproduct formation after 120 h (Table 1, entry 7). It was also observed that the molar ratio of the reactants was an important variable. By increasing the amount of $NH_4OH$, the reaction yielded more products regardless of whether microwave activation or ambient temperature stirring was applied. Thus, to achieve practical reaction times, it was decided that a 10 fold molar excess of the reagent would be used to improve the rate of the ambient temperature reaction. At such excess the reaction was completed in 3 h requiring only stirring. While the green chemistry principles are against the use of excess chemicals, in the current example the product is easily separated from the aqueous phase, thus the remaining $NH_4OH$ can be readily recycled. Most importantly, however, the data unambiguously indicate that the formation of pyrrole does not require the application of a catalyst.

While the data in Table 1 were obtained in small scale experiments, an effort was made to scale up the process. Based on the data presented above, considering the benefits and disadvantages of different systems, ambient temperature reaction conditions have been selected. In this reaction 0.114 g of hexane-2,5-dione was added to 1.29 mL 28-30% aqueous $NH_4OH$. The reaction appeared to proceed efficiently yielding 75% isolated product suggesting that the process can be scaled up to practical levels.

After the successful completion of the Paal-Knorr reaction with aqueous $NH_4OH$ to underivatized pyrrole, our attention turned toward extending the scope of the reaction. Three groups of amines were considered: aliphatic amines (including cyclic and benzylic amines), aromatic amines (e.g. anilines) and diamines. Similarly to Table 1, an extensive optimization was carried out for all three groups of amines with similar results. While microwave irradiation appeared to be more effective with primary amines than with $NH_4OH$, yielding quantitative reactions, it required elevated temperatures (e.g. 120 ˚C). It was also observed, that the room temperature reactions provided equally high yields in relatively short times. Thus, further reactions were carried out with simple stirring at RT. Due to the higher reactivity of amines, the reactions can be carried out at a 1:1 molar ratio. It is particularly advantageous; since the reaction is selective and quantitative, the products form exclusively, thus no purification is required. Using excess amine, the separation of the remaining amine from the pyrrole would add an unnecessary purification step. In addition, it was observed that the presence of the solvent was not mandatory. Since both the ketone and the amines are liquids at room temperature and perfectly miscible with each other, the

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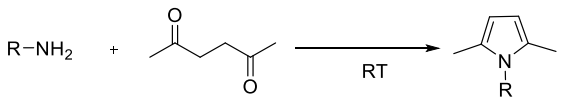
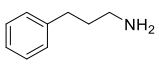
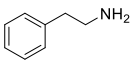
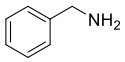
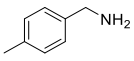
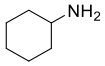
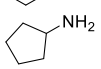
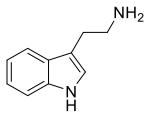
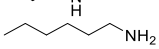
reaction could be carried out in a solvent-free environment using the neat reactants. Therefore, based on the second optimization carried out with amines, the neat reaction at room temperature was selected as the most effective and environmentally benign reaction condition for further pyrrole synthesis.

First, the Paal-Knorr type pyrrole synthesis using alkylamines was carried out. The reactions resulted in excellent yields, with quantitative conversions in 5-10 min, as tabulated in Table 2. As the carbon number of the amino-bearing carbon chain increases, the reaction time is shortened (Table 2, entries 1-3). As the longer chain farther removes the electron withdrawing effect of the phenyl groups from the $NH_2$, these data are in line with the increased reactivity of primary phenyl-alkylamines. The reactions of the acyclic alkyl or benzylamines (Table 2 entries 1-4, 7,8) are much faster than those of the cycloalkyl amines (entries 5, 6), due to steric hindrance caused by the rings immediately attached to the amino group that significantly decrease its nucleophilicity as compared to linear analogues.

**Table 2.** Reaction of hexan-2,5-dione with alkyl-, cycloalkyl- and benzylamines[a]



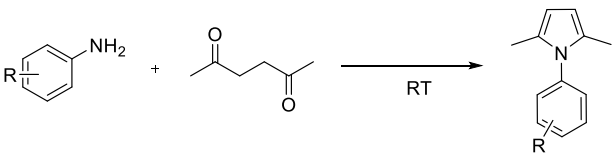

| Entry | amine | Time (min) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  | 5 | 100 | 97 |
| 2 |  | 7 | 100 | 98 |
| 3 |  | 10 | 88 | 81 |
| 4 |  | 10 | 100 | 96 |
| 5 |  | 24[b] | 100 | 96 |
| 6 |  | 24[b] | 100 | 97 |
| 7 |  | 5 | 100 | 97 |
| 8 |  | 7 | 100 | 98 |

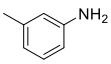
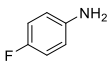
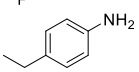
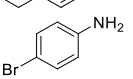
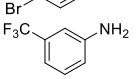
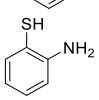
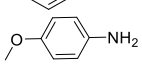
[a] 1mmol amine, 1 mmol diketone, both neat, mixed and stirred at room temperature
[b] reaction time is given in h

The conversion of the starting materials was nearly quantitative providing the products in high isolated yields indicating the versatility of the reaction.

After the successful experiments with alkylamines, the scope was extended to aromatic amines, for example anilines. In order to observe the effect of substituents, a variety of anilines with electron-donating and electron-withdrawing groups were used (Table 3). These reactions were also carried out at room temperature without any solvent or catalyst resulting in very good to excellent yields. As expected the reaction of anilines required significantly longer time to complete than that of the alkylamines (with the exception of cycloalkyl amines, Table 2 entries 5, 6). It can also be observed, that despite the longer reaction times, the yields are mostly not as high as in Table 2. This is due to the decreased basicity and nucleophilicity of the aniline amino group, which is caused by multiple factors. First, the electron withdrawing nature of the phenyl ring decreases the electron density on the N. The direct attachment of the ring to the $NH_2$ group sterically hinders the attack on the N and also decreases reactivity. Based on the analysis of the yields, the substituents of the phenyl ring did not appear to have a noteworthy effect on the reactions, except $OCH_3$, in which case the reaction time was noticeably shorter (4 h *vs.* 24h).

**Table 3.** Reaction of hexan-2,5-dione with substituted anilines[a]




| Entry | aniline | Time (h) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  | 24 | 83 | 80 |
| 2 |  | 24 | 76 | 70 |
| 3 |  | 24 | 92 | 87 |
| 4 |  | 24 | 92 | 90 |
| 5 |  | 24 | 71 | 65 |
| 6 |  | 24 | 88 | 80 |
| 7 |  | 21 | 91 | 87 |
| 8 |  | 4 | 100 | 94 |

[a] 1mmol aniline, 1 mmol diketone, both neat, mixed and stirred at room temperature

To further extend the scope of the reaction, the Paal-Knorr type pyrrole synthesis was investigated with diamines (Table 4). Based on the above data, it is expected that the diamines will react with 2,5-hexanedione. The major question to be answered was how these reactions occur. Using a diamino

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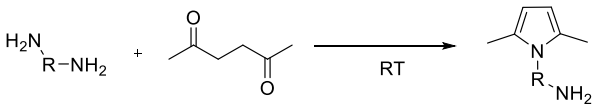
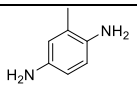
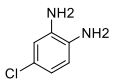
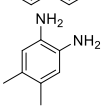
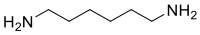
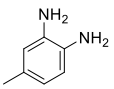
compound as the reactant with 2,5-hexandione may result in the formation of multiple products. The potential possibilities were the formation of a single pyrrole (only one $NH_2$ reacts with 1 mol of diketone) a double pyrrole (both $NH_2$ groups react with 2 mol diketone) or the two amino groups would react with the two carbonyl groups in a 1:1 molar ratio, respectively and form a C8 ring.

During the optimization of the diamine-dione reaction it was observed that the reaction selectively resulted in the formation of the mono-pyrrole product. The mono-pyrrole was the exclusive product even when an excess amount of 2,5-hexanedione was used. 1,6-Diaminohexane was the only exception to this rule; it gave bis-pyrrole product when an excess amount of 2,5-hexanedione was applied. However, at 1:1 reactant ratios both mono-pyrrole and di-pyrrole were produced. The previously described difference in reactivity was observed here as well; the aliphatic diamine (Table 4, entry 6) reacted at a higher rate than that of the aromatic diamines (Table 4, entries 1-5, 7) and provided the expected products in a shorter time, as well as in higher yield. The selective mono-pyrrole formation of phenylene-diamine regioisomers results in potentially useful building blocks, that possess an underivatized primary amino group that can be used to attach the products to other structures as needed.

**Table 4.** Reaction of hexan-2,5-dione with aliphatic and aromatic diamines[a]



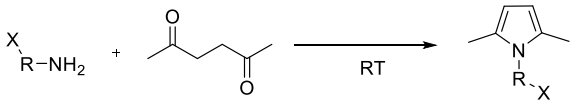

| Entry | | Time (h) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  | 24 | 80 | 77 |
| 2 |  | 24 | 68 | 61 |
| 3 |  | 24 | 78 | 57 |
| 4 |  | 24 | 81 | 72 |
| 5 |  | 24 | 87 | 79 |
| 6 |  | 0.083 | 100 | 96[b] |
| 7 |  | 24 | 83 | 80 |

[a] 1mmol diamine, 1 mmol diketone, both neat, mixed and stirred at room temperature

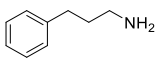
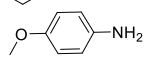
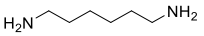
[b] bis-pyrrole product with excess of the diketone

While the above reactions were carried out using 1 mmol of the reactants each, a possible scale-up of the process was also attempted. The amounts of the reactants were increased to 10 mmol, about 1.2-2 g of the amine and the diketone, respectively (Table 5). It was observed that the selected larger scale reactions occurred with similar efficiency as their previous counterparts. In fact, all three reactions gave nearly quantitative yields. The exclusive selectivity, obtained under mild conditions, made the usual extra isolation step unnecessary, resulting in only negligible loss of product. While usually scaling up a procedure requires longer reaction time, the data showed that no significant increase in reaction time was necessary in order to scale up the reaction by a factor of 10. These results indicate that the further scale up of the reaction is most likely possible.

**Table 5.** Scale-up of the reaction of hexan-2,5-dione with primary amines[a]




R = alkyl, aryl; X = H, $NH_2$

| Entry | amine | Time (min) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  | 5 | 100 | 99 |
| 2 |  | 240 | 100 | 99 |
| 3 |  | 5 | 100 | 99[b] |

[a] 10 mmol amine (1.2-2 g), 10 mmol diketone, both neat, mixed and stirred at room temperature

[b] 10 mmol amine, 20 mmol diketone, the isolated yield is that of the bis-pyrrole product formed

After studying pyrrole synthesis using 2,5-hexanedione and a broad variety of amines of different types our attention turned toward the applicability of other appropriate (1,4 dicarbonyl) diketones. Several commercially available diketones have been applied with a smaller but representative group of amines. The results are tabulated in Table 6.

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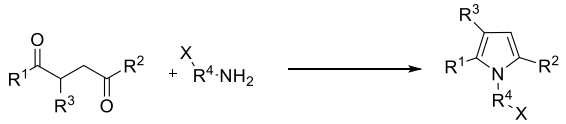
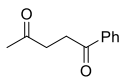
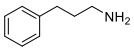
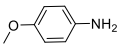
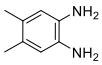
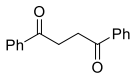
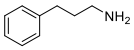
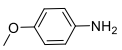
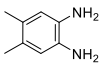
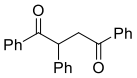
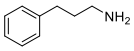
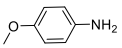
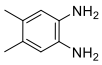
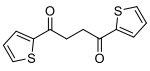
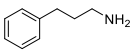
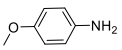
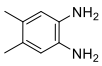
**Table 6.** Reaction of various diones with amines and diamines[a]




| | diketone | amine | Time (h) | T (˚C) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | 5 min | RT | 90 | 72 |
| 2 | |  | 24 | RT | 97 | 88 |
| 3 | |  | 24 | RT | 99 | 92 |
| 4 | | $NH_4OH$ | 5 | RT | 100 | 98 |
| 5 |  |  | 48 | 100 | 89 | 72 |
| 6 | |  | 80 | 100 | 80 | 70 |
| 7 | |  | 80 | 100 | 71 | 64 |
| 8 |  |  | 50 | 100 | 88 | 72 |
| 9 | |  | 72 | 100 | 55 | 42 |
| 10 | |  | 72 | 100 | 74 | 56 |
| 11 |  |  | 48 | 100 | 91 | 79 |
| 12 | |  | 80 | 100 | 37 | 32 |
| 13 | |  | 80 | 100 | 71 | 65 |

[a] 1mmol diamine, 1 mmol diketone, both neat, mixed and stirred at the desired temperature

In selecting the diketones, a simple approach was followed: 2,5-hexanedione possesses methyl groups as end groups $R^1$ and $R^2$. Thus, the emphasis was placed on substituting the alkyl groups with phenyl and observing the effect of structure on the performance of the reaction. First, one methyl group was substituted as $R^1$ (1-phenylpentane-1,4-dione), then another (both $R^1$ and $R^2$ are Phe, 1,4-diphenylbutane-1,4-dione) and then three ($R^1$, $R^2$, $R^3$=Phe, 1,2,4-triphenylbutane-1,4-dione). Finally, another di-heteroaryl diketone ($R^1$, $R^2$=thiophen-2-yl, 1,4-di(thiophen-2-yl)butane-1,4-dione) was selected to observe the effect of a heteroaryl ring. The data indicate that the catalyst and solvent free system is mostly effective for carrying out the Paal-Knorr reaction. It is also apparent that the structure of the dione has a significant effect on its reactivity. Replacing one terminal methyl group ($R^1$ = Phe, 1-phenylpentane-1,4-dione, Table 6, entries 1-4) to phenyl does not appear to significantly affect the reactivity of the diketone, thus the reaction times and temperature are similar to those observed in the reaction of 2,5-hexanedione with the same amines (Tables 1-4). It is worth mentioning, that the reaction readily occurred with aq. $NH_4OH$ as well. Despite the mild conditions, all reactions provided the products in high to excellent yields. Replacing both terminal methyl groups ($R^1$, $R^2$ = Phe, 1,4-diphenylbutane-1,4-dione, Table 6, entries 5-7), however, resulted in reasonable decrease in the activity of the diketone. While the pyrrole synthesis readily progressed with alkyl or aryl-amines as well as, 4,5-dimethyl-*o*-phenylene diamine, the reaction required elevated temperature and long reaction time. The reaction, however, did not proceed with $NH_4OH$, even at elevated temperatures most likely due to the rapid release of $NH_3$ gas from the solution. Nonetheless, despite the decreasing activity the N-substituted products were obtained in good yields. Adding a third phenyl group to the substrate ($R^1$, $R^2$, $R^3$=Phe, 1,2,4-triphenylbutane-1,4-dione, Table 6 entries 8-10) further decreased the reactivity. The product formation required long reaction times at elevated temperature and the observed yields are moderate to good. Replacing the terminal groups to an electron rich thiophen-2-yl ($R^1$, $R^2$=thiophen-2-yl, 1,4-di(thiophen-2-yl)butane-1,4-dione, Table 6 entries 11-13) resulted in similar performance to the diphenyl analog (Table 6, entries 5-7). The reaction proceeded at 100 ˚C, required considerable time and yielded the expected pyrroles in moderate to high yields.

The experiments with the various diketones suggest a generic pattern; terminal methyl and potentially alkyl groups perform well in the reaction even at room temperature. Increasing the complexity of the compounds by replacing the terminal methyl groups with larger and electron withdrawing phenyl groups appears to gradually decrease the reactivity of the diketone and the reaction requires elevated temperature and extended reaction times.

Based on the above presented data the synthetic utility of the method appears broadly applicable. Several amines of different types as well as ammonia (in the form of the conveniently available $NH_4OH$) were proven to be useful substrates for the reaction with a variety of 1,4-diketones. However, none of the compounds in the above Tables contained acid labile functional groups. As often times reactions are carried out in the presence of acid labile protecting groups[23] it is important to investigate whether the above reaction conditions are applicable for compounds with such acid sensitive functional groups.

Therefore a study has been carried out on the stability of such substituents under the current catalyst and solvent free conditions. We have selected four amines and two 1,4-dicarbonyl compounds to observe whether the protecting groups would be removed. The data are tabulated in Table 7.

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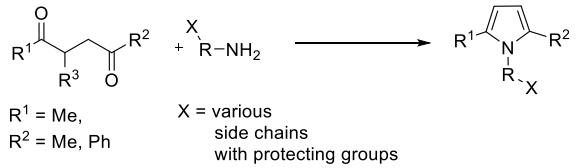
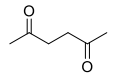
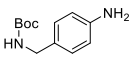
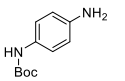
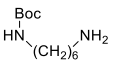
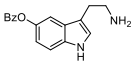
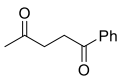
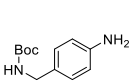
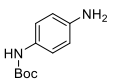
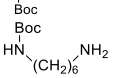
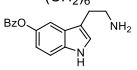
**Table 7.** Reaction of various diones with amines and diamines possessing protecting groups[a]




| | diketone | amine | Time (h) | T (˚C) | GC Yield (%) | Isolated Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | 24 | RT | 98 | 91 |
| 2 | |  | 24 | RT | 89 | 84 |
| 3 | |  | 15 min | RT | 99 | 97 |
| 4 | |  | 15 min | RT | 100 | 96 |
| 5 |  |  | 24 | 100 | 82 | 73 |
| 6 | |  | 24 | 100 | 95 | 91 |
| 7 | |  | 3 | 100 | 92 | 88 |
| 8 | |  | 3 | 100 | 94 | 93 |

[a] 1mmol diamine, 1 mmol diketone, both neat, mixed and stirred at the desired temperature, the protecting groups remained in the products and no deprotected product was observed.

Table 7 indicates that the protected amines and hydroxyl compound underwent the cyclization reaction without any difficulty and the expected products were isolated in good to excellent yields. In all cases the acid labile protecting groups remained in the product indicating that the methods tolerates these functional groups. Therefore, it appears that the method can be expanded to such compounds, which only adds to the advantages of our catalyst and solvent-free reaction process.

Analyzing the mechanism of the reaction provides an explanation for this phenomenon. Being classical and well-studied, the mechanism of the Paal-Knorr reaction has been thoroughly studied.[24] It is reasonable to propose that the transformations in the current work follow a different mechanism than that described in our earlier catalytic pyrrole synthesis under strongly acidic conditions.[19-21] The proposed current mechanism is summarized in Fig. 7.

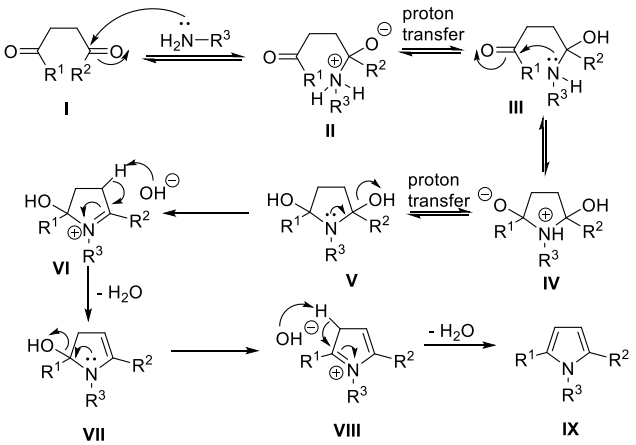



**Figure 7** The proposed mechanism of the non-catalytic Paal-Knorr cyclization of 1,4-diones with aqueous ammonium hydroxide ($R^3$=H) and primary amines

Accordingly, it is suggested that the carbonyl group reacts with the amino group to form the hemiaminal (Fig. 7, **III**). Amarath *et al.* described[24] that *meso*- and *dl*-3,4-diethyl-2,5-hexanediones cyclize at different rates, and that the stereochemistry of the unchanged dione is preserved during the reaction. These observations led to the conclusion that under non-acidic conditions the formation of an enamine intermediate can be ruled out. In contrast, under typical acidic conditions the hemiaminal could undergo a loss of water and the subsequent formation of an imine that could isomerize to an enamine, which could initiate the cyclization. Thus we propose that as a next step, the hemiaminal attacks the other carbonyl to cyclize to 2,5-dihydroxy-2,5-dialkyl-N-alkyl-hydropyrrole (Fig. 7, **V**), which, step-by–step, undergoes a double water elimination to give the corresponding N-substituted pyrrole. Use of ammonium hydroxide instead of amines gives the underivatized NH containing pyrrole. In the above mentioned studies[24] it was reported that the substituents on the aryl end-groups (Fig. 7, **I**, $R^1$, $R^2$) had a reasonable effect on the reaction. A similar phenomenon was observed in the current work as well. When at least one terminal group (Fig. 7, **I**, $R^1$or $R^2$) was methyl (dimethyl- and methyl/phenyl) the reaction readily progressed at room temperature, while when both terminal groups were phenyl, the reaction required heating and provided lower yields. If $R^2$ in the hemiaminal is Me (Fig. 7, **III**) its electron donating effect would enhance the electron density on the N, thus facilitating the cyclization. $R^1$ of **III** appears unimportant as indicated by the similar reaction rates of the two diketones (Tables 1-4 and Table 6 entries1-4). However, when both $R^1$ and $R^2$ are Phe, the electron withdrawing nature of the phenyl group would decrease the electron density of the N and the availability of the lone pair of the nitrogen. Thus, in such cases, the cyclization requires higher activation energy than that provided by RT to occur.

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The procedure presented above allows the use of a wide variety of amines with diketones in the Paal-Knorr reaction, including aqueous $NH_4OH$, alkyl- or cycloalkyl amines, anilines and various diamines. It was observed that the pyrrole synthesis occurred in high yields without a catalyst or a solvent. The reaction represents the ultimate green synthesis of a large number of 2,5-substituted-pyrroles and possessing the following major advantages: (i) other than the starting materials, the reaction occurs without the use of any additional reagent or catalyst, thus the catalyst recycling or the reagent disposal do not need to be considered; (ii) the starting materials react under "neat" conditions, without the presence of a solvent, thus any hazard related to solvents or the cost of solvent recycling are eliminated; (iii) the reaction, in most cases, occurs with nearly quantitative conversions and provides high isolated yields; (iv) the starting materials react in 1:1 ratio, no excess of either one is required for good yields; (iv) the atom economy of the process is around 90% (the exact value is dependent on the molecular mass of the amines) and the only byproduct that forms is $H_2O$; (v) in most cases the process is truly "solvent-free", namely no solvent is needed to isolate the products; (vi) in several cases no further purification step is necessary to obtain pure products, a simple drying will eliminate the byproduct water; (vii) the reactions all occur at room temperature, which is convenient, safe and energy efficient finally (viii) the process appeared to tolerate acid labile protecting groups as well.

## Conclusions

A simple, selective and environmentally benign synthesis of dimethyl-pyrroles is described. The reaction of 1,4-diones with aqueous ammonium hydroxide and a broad variety of amines provides high yields under mild conditions. The major advantages of this approach are: high atom economy, catalyst and solvent-free reaction, limited energy consumption (short reaction time and generally no heating needed) and its waste-free nature as $H_2O$ is the only byproduct.

## Experimental Section

**Materials:** All amines and 2,5-hexanedione were purchased from Aldrich and used without any purification. $CDCl_3$ used as a solvent (99.8%) for NMR studies was an Aldrich product. Ethyl acetate used for product isolation in the $NH_4OH$ reactions (minimum purity of 99.5%) was a Fisher product.

**NMR Analysis:** The $^1H$ and $^{13}C$ spectra were obtained on a 300 MHz Varian NMR spectrometer, in $CDCl_3$ with either using the signal of tetramethylsilane or the residual solvent signal as standards. The temperature was 25 °C (accuracy ±1 °C) and controlled by the Varian control unit.

**GC-MS Analysis:** The mass spectrometric identification of the products have been carried out by an Agilent 6850 gas chromatograph- 5973 mass spectrometer system (70 eV electron impact ionization) using a 30m long DB-5 type column (J&W Scientific).

**General Procedure:** Amine (10 mmol) and 2,5-hexanedione (10 mmol) were mixed and stirred in a 25ml round-bottom flask at room temperature. After the reaction was complete, the product was placed under vacuum to remove the byproduct water. The products were isolated as low melting crystals or oils. NMR and GC-MS confirmed the identity of the products and indicated the sufficient purity (> 95% and no water according to the $^1H$ NMR)

**2,5-dimethyl-1-(3-phenylpropyl)-1H-pyrrole** (Table 2 entry 1)
Dark brown oil; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.20-7.06 (m, 5H), 5.67 (s, 2H), 3.62 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.06 (s, 6H), 1.83 (quintet, *J* = 7.5 Hz, 2H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 140.9, 128.3, 128.1, 127.0, 125.9, 104.9, 42.8, 32.9, 32.1, 12.3; **MS**-$C_{15}H_{19}N$ (213) m/z (%): 213 ($M^+$, 100), 108 (100), 109 (72), 94 (34), 92 (23).

**2,5-dimethyl-1-(2-phenylethyl)-1H-pyrrole** (Table 2 entry 2)
Dark brown oil; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.49-7.43 (m, 3H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.01 (s, 2H), 4.13 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 6H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 138.3, 128.6, 128.3, 127.0, 126.4, 105.0, 45.0, 37.3, 12.1; **MS**-$C_{14}H_{17}N$ (199) m/z (%): 199 ($M^+$, 100), 108 (92), 200 (16), 104 (10), 77 (8).

**1-benzyl-2,5-dimethyl-1H-pyrrole** (Table 2 entry 3)
Dark brown crystal, MP = 45°C; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.42-7.32 (m, 3H), 7.00 (d, *J* = 9.0 Hz, 2H), 5.99 (s, 2H), 5.11 (s, 2H), 2.25 (s, 6H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 138.4, 128.5, 127.7, 126.8, 125.4, 105.3, 46.5, 12.3; **MS**-$C_{13}H_{15}N$ (185) m/z (%): 185 ($M^+$, 72), 91 (100), 65 (15), 92 (15).

**2,5-dimethyl-1-(4-methylbenzyl)-1H-pyrrole** (Table 2 entry 4)
Brown crystal, MP = 44-47°C; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.13 (d, *J* = 6.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.89 (s, 2H), 5.00 (s, 2H), 2.34 (s, 3H), 2.17 (s, 6H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 136.4, 135.4, 129.3, 127.8, 125.5, 105.2, 46.4, 20.9, 12.4; **MS**-$C_{14}H_{17}N$ (199) m/z (%): 119 ($M^+$, 81), 105 (100), 200 (12), 77 (9), 106 (9).

**1-cyclohexyl-2,5-dimethyl-1H-pyrrole** (Table 2 entry 5)
Dark brown oil; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 5.65 (s, 2H), 3.85-3.76 (m, 1H), 2.21 (s, 6H), 1.88-1.63 (m, 8H), 1.27-1.09 (m, 2H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 127.7, 105.9, 56.3, 32.3, 26.6, 25.6, 14.3; **MS**-$C_{12}H_{19}N$ (177) m/z (%): 177 ($M^+$, 100), 94 (90), 95 (70), 96 (18), 55 (12).

**1-cyclopentyl-2,5-dimethyl-1H-pyrrole** (Table 2 entry 6)
Dark brown oil; **$^1H$ NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 5.77 (s, 2H), 4.54 (quintet, *J* = 9.0 Hz, 1H), 2.30 (s, 6H), 2.04-1.88 (m, 6H), 1.71-1.66 (m, 2H); **$^{13}C$ NMR** (75.474 MHz, $CDCl_3$), δ

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(ppm) 127.8, 105.8, 56.1, 31.1, 24.9, 14.0; **MS**-$C_{11}H_{17}N$ (163) m/z (%): 163 ($M^+$, 46), 94 (100), 95 (58), 96 (17), 80 (16).

**3-(2-(2,5-dimethyl-1H-pyrrol-1-yl)ethyl)-1H-indole** (Table 2 entry 7)
Brown crystal, mp = 85°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.88 (s, br, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.35-7.20 (m, 3H), 6.85 (s, 1H), 5.92 (s, 2H), 4.08 (t, *J* = 7.5 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.29 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 136.0, 127.4, 127.0, 122.0, 121.9, 119.3, 118.3, 112.3, 111.2, 105.0, 44.2, 26.7, 12.4; **MS**-$C_{16}H_{18}N_2$ (238) m/z (%): 238 ($M^+$, 91), 130 (100), 108 (25), 143 (19), 239 (17).

**1-hexyl-2,5-dimethyl-1H-pyrrole** (Table 2 entry 8)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 5.85 (s, 2H), 3.79 (t, *J* = 9.0 Hz, 2H), 2.30 (s, 6H), 1.72-1.64 (m, 2H), 1.42 (m, 6H), 1.00 (t, *J* = 7.5 Hz, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 127.0, 104.8, 43.5, 31.4, 30.9, 26.5, 22.5, 13.9, 12.3; **MS**-$C_{12}H_{21}N$ (179) m/z (%): 179 ($M^+$, 86), 108 (100), 109 (66), 94 (35), 122 (31).

**2,5-dimethyl-1-phenyl-1H-pyrrole** (Table 3 entry 1)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.45-7.33 (m, 3H), 7.18 (d, *J* = 6.0 Hz, 1H), 5.88 (s, 2H), 2.00 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 138.9, 130.0, 129.0, 128.7, 128.2, 127.6, 105.6, 12.7; **MS**-$C_{12}H_{13}N$ (171) m/z (%): 171 ($M^+$, 80), 170 (100), 77 (14), 154 (11), 156 (10).

**2,5-dimethyl-1-(m-tolyl)-1H-pyrrole** (Table 3 entry 2)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.32-7.00 (m, 4H), 5.89 (s, 2H), 2.39 (s, 3H), 2.03 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 138.9, 138.8, 128.8, 128.7, 128.3, 125.1, 105.4, 21.2, 13.0; **MS**-$C_{13}H_{15}N$ (184) m/z (%): 184 ($M^+$, 100), 185 (77), 170 (11), 168 (10), 186 (10).

**1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole** (Table 3 entry 3)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.15-7.07 (m, 4H), 5.86 (s, 2H), 1.98 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 163.4, 160.1, 129.8, 128.8, 116.1, 115.8, 105.7, 12.9; **MS**-$C_{12}H_{12}FN$ (189) m/z (%): 189 ($M^+$, 83), 188 (100), 95 (13), 174 (12), 172 (10).

**1-(4-ethylphenyl)-2,5-dimethyl-1H-pyrrole** (Table 3 entry 4)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.30 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 5.93 (s, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.07 (s, 6H), 1.32 (t, *J* = 7.5 Hz, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 143.5, 136.4, 128.3, 127.9, 115.1, 105.3, 28.4, 15.4, 12.9; **MS**-$C_{14}H_{17}N$ (199) m/z (%): 199 ($M^+$, 93), 198 (100), 143 (17), 154 (15), 200 (13).

**1-(4-bromophenyl)-2,5-dimethyl-1H-pyrrole** (Table 3 entry 5)
Brown needle, MP = 75°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.60 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 5.92 (s, 2H), 2.04 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 138.0, 132.3, 129.8, 128.6, 121.5, 106.0, 13.0; **MS**-$C_{12}H_{12}BrN$ (250) m/z (%): 250 ($M^+$, 97), 249 (100), 251 (95), 248 (92), 154 (50).

**2,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrrole** (Table 3 entry 6)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.61-7.33 (m, 4H), 5.85 (s, 2H), 1.96 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 131.6, 129.7, 129.2, 128.7, 128.3, 125.2, 124.4, 118.2, 106.4, 13.0; **MS**-$C_{13}H_{12}F_3N$ (239) m/z (%): 239 ($M^+$, 69), 238 (100), 145 (11), 224 (10), 240 (9).

**2-(2,5-dimethyl-1H-pyrrol-1-yl)benzenethiol** (Table 3 entry 7)
Yellow powder, MP = 111-116°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.50 (d, *J* = 9.0 Hz, 1H), 7.32-7.22 (m, 2H), 7.13 (d, *J* = 6.0 Hz, 1H), 5.93 (s, 2H), 4.2 (broad, 1H), 1.93 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 173.5, 136.8, 136.1, 129.3, 128.5, 127.1, 126.0, 117.0, 106.2, 12.6; **MS**-$C_{12}H_{13}NS$ (203) m/z (%): 203 ($M^+$, 53), 188 (100), 186 (42), 200 (25), 173 (17).

**1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole** (Table 3 entry 8)
Brown needle, MP = 58°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.12 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H) 5.87 (s, 2H), 3.83 (s, 3H), 2.01 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 158.7, 131.5, 129.0, 128.8, 114.0, 105.1, 55.2, 12.8; **MS**-$C_{13}H_{15}NO$ (201) m/z (%): 201 ($M^+$, 100), 200 (67), 186 (24), 125 (18), 202 (13).

**4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-methylaniline** (Table 4 entry 1)
Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.09 (d, *J* = 6.0 Hz, 1H), 6.54-6.47 (m, 2H), 5.87 (s, 2H), 3.66 (s, br, 2H), 2.19 (s, 3H), 2.04 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 144.9, 137.6, 130.6, 128.6, 121.5, 118.0, 114.2, 105.0, 17.0, 12.8; **MS**-$C_{13}H_{16}N_2$ (200) m/z (%): 200 ($M^+$, 100), 199 (88), 144 (17), 201 (16), 185 (16).

**2-(2,5-dimethyl-1H-pyrrol-1-yl)aniline** (Table 4 entry 2)
Black needle, MP = 70-73°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.17-7.10 (m, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.74-6.69 (m, 2H), 5.85 (s, 2H), 3.37 (s, br, 2H), 1.90 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 144.1, 129.3, 129.3, 128.4, 124.4, 118.2, 115.5, 105.8, 12.3; **MS**-$C_{12}H_{14}N_2$ (186) m/z (%): 186 ($M^+$, 66), 171 (100), 132 (37), 131 (28), 185 (20).

**5-chloro-2-(2,5-dimethyl-1H-pyrrol-1-yl)aniline** (Table 4 entry 3)
Tan powder, MP = 87-90°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 6.90 (d, *J* = 9.0 Hz, 1H), 6.71-6.66 (m, 2H), 5.85 (s, 2H), 3.45 (s, br, 2H), 1.89 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 145.2, 134.7, 130.3, 128.4, 122.8, 118.1, 115.1, 106.2, 12.3; **MS**-$C_{12}H_{13}ClN_2$ (220) m/z (%): 220 ($M^+$, 67), 205 (100), 207 (32), 222 (17), 219 (16).

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**8-(2,5-dimethyl-1H-pyrrol-1-yl)naphthalen-1-amine** (Table 4 entry 4)

Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.18-7.05 (m, 6H), 6.25 (d, *J* = 9.0 Hz, 2H), 3.97 (s, br, 2H), 1.08 (s, 6H); **$^{13}$C NMR**(75.474 MHz, $CDCl_3$), δ (ppm) 145.6, 137.2, 129.0, 128.0, 127.5, 125.2, 124.9, 121.9, 117.9, 115.4, 113.4, 103.3, 11.6; **MS**-$C_{16}H_{16}N_2$ (236) m/z (%): 236 ($M^+$, 58), 221 (100), 206 (41), 222 (17), 205 (15).

**2-(2,5-dimethyl-1H-pyrrol-1-yl)-4,5-dimethylaniline** (Table 4 entry 5)

Black crystal, MP = 80-83°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 6.71 (s, 1H), 6.51 (s, 1H), 5.82 (s, 2H), 3.16 (s, br, 2H), 2.13 (s, 3H), 2.07 (s, 3H), 1.89 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 141.6, 137.6, 129.8, 128.4, 126.3, 122.0, 117.0, 105.5, 19.6, 18.7, 12.4; **MS**-$C_{14}H_{18}N_2$ (214) m/z (%): 214 ($M^+$, 51), 199 (100), 200 (15), 213 (14), 197 (11).

**1,6-bis(2,5-dimethyl-1H-pyrrol-1-yl)hexane** (Table 4 entry 6)

Ivory powder, MP = 104-105°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 5.86 (s, 4H), 3.81 (t, *J* = 7.5 Hz, 4H), 2.31 (s, 12H), 1.75-1.70 (m, 4H), 1.50-1.47 (m, 4H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 127.1, 104.9, 43.4, 30.9, 26.6, 12.4; **MS**-$C_{18}H_{28}N_2$ (272) m/z (%): 272 ($M^+$, 100), 108 (39), 164 (33), 109 (31), 273 (20).

**2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methylaniline** (Table 4 entry 7)

Dark brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 6.88 (d, *J* = 9.0 Hz, 1H), 6.58-6.55 (m, 2H), 5.88 (s, 2H), 3.33 (s, br, 2H), 2.28 (s, 3H), 1.94 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 143.7, 139.2, 129.8, 129.5, 128.9, 119.1, 116.1, 105.6, 21.3, 12.3; **MS**-$C_{12}H_{20}N_2$ (200) m/z (%): 200 ($M^+$, 70), 185 (100), 199 (19), 183 (14), 186 (14).

**2-methyl-5-phenyl-1-(3-phenylpropyl)-1H-pyrrole** (Table 6 entry 1)

Dark yellow oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.34-7.15 (m, 8H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.10 (d, *J* = 3.0 Hz, 1H), 5.95 (d, *J* = 3.0 Hz, 1H), 3.88 (t, *J* = 7.5 Hz, 2H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 3H), 1.87 (quin, *J* = 7.5 Hz, 2H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 140.88, 134.24, 133.78, 128.82, 128.32, 128.30, 128.11, 126.53, 125.90, 107.84, 106.76, 43.53, 32.73, 32.16, 12.63; **MS**-$C_{20}H_{21}N$ (275) m/z (%): 275 ($M^+$, 40), 170 (100), 171 (28), 91 (15), 156 (12).

**1-(4-methoxyphenyl)-2-methyl-5-phenyl-1H-pyrrole** (Table 6 entry 2)

Ivory solid, MP = 107°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.13-7.00 (m, 7H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.31 (d, *J* = 6.0 Hz, 1H), 6.40 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 2.08 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 158.54, 134.14, 133.52, 132.13, 131.87, 129.34, 127.88, 127.64, 125.50, 114.05, 108.25, 107.11, 55.32, 13.21; **MS**-$C_{18}H_{17}NO$ (263) m/z (%): 263 ($M^+$, 100), 207 (26), 262 (22), 248 (21), 264 (20).

**4,5-dimethyl-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)aniline** (Table 6 entry 3)

Dark yellow oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.21-7.02 (m, 5H), 6.77 (s, 1H), 6.49 (s, 1H), 6.40 (d, *J* = 3.0 Hz, 1H), 6.09 (d, *J* = 3.0 Hz, 1H), 3.28 (s, br, 2H), 2.16 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 141.33, 137.59, 133.39, 133.35, 131.93, 129.98, 128.00, 126.62, 126.45, 125.57, 122.69, 117.22, 108.41, 107.36, 19.61, 18.69, 12.49; **MS**-$C_{19}H_{20}N_2$ (276) m/z (%): 276 ($M^+$, 100), 261 (75), 275 (32), 277 (21), 199 (20).

**2-methyl-5-phenyl-1H-pyrrole** (Table 6 entry 4)

Pink solid, MP = 81°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 8.11 (s, br, 1H), 7.37 (d, *J* = 6.0 Hz, 2H), 7.27 (t, *J* = 7.5Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 2.26 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm); 132.88, 131.09, 128.74, 127.95, 125.56, 123.27, 107.85, 106.09, 13.12 **MS**-$C_{11}H_{11}N$ (157) m/z (%): 157 ($M^+$, 71), 156 (100), 128 (11), 77 (8), 158 (7).

**2,5-diphenyl-1-(3-phenylpropyl)-1H-pyrrole** (Table 6 entry 5)

Yellow oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.36-7.19 (m, 11H), 6.97 (m, 2H), 6.69-6.66 (m, 2H), 6.19 (s, 2H), 4.00 (t, *J* = 7.5 Hz, 2H), 2.03 (t, *J* = 7.5 Hz, 2H), 1.44 (quin, *J* = 7.5 Hz, 2H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 140.91, 136.47, 134.00, 128.87, 128.45, 128.15, 127.94, 126.86, 125.62, 109.50, 44.74, 32.33, 31.80; **MS**-$C_{25}H_{23}N$ (337) m/z (%): 337 ($M^+$, 52), 232 (100), 233 (27), 91 (16), 338 (14).

**1-(4-methoxyphenyl)-2,5-diphenyl-1H-pyrrole** (Table 6 entry 6)

Off white solid, MP = 223°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.18-7.00 (m, 10H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.40 (s, 2H), 3.71 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 158.59, 136.05, 133.46, 132.02, 129.94, 128.81, 128.02, 126.26, 114.06, 109.78, 55.49; **MS**-$C_{23}H_{19}NO$ (325) m/z (%): 325($M^+$, 100), 326 (24), 207 (17), 310 (12), 178 (10).

**2-(2,5-diphenyl-1H-pyrrol-1-yl)-4,5-dimethylaniline** (Table 4 entry 7)

Pale yellow solid, MP = 189-190°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.15-7.10 (m, 10H), 6.69 (s, 1H), 6.49 (s, 1H), 6.37 (s, 2H), 3.24 (s, br, 2H), 2.09 (s, 3H), 1.96 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 141.26, 137.68, 135.68, 133.07, 130.58, 127.94, 127.89, 126.59, 126.18, 122.68, 117.42,

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109.83, 19.68, 18.71; **MS**-$C_{24}H_{22}N_2$ (338) m/z (%): 338 ($M^+$, 100), 234 (28), 337 (26), 339 (24), 261 (13).

**2,3,5-triphenyl-1-(3-phenylpropyl)-1H-pyrrole** (Table 6 entry 8)

Yellow oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.52-7.34 (m, 9H), 7.26-7.09 (m, 9H), 6.79 (dd, *J* = 4.5 Hz, 2H), 6.51 (s, 1H), 3.97 (t, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 1.59 (quin, *J* = 7.5 Hz, 2H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 140.77, 136.24, 135.14, 133.72, 133.30, 131.91, 131.14, 129.94, 129.60, 129.47, 129.17, 127.99, 127.89, 127.65, 127.56, 127.02, 125.64, 125.00, 122.96, 109.49, 44.45, 32.43, 31.72; **MS**-$C_{31}H_{27}N$ (413) m/z (%): 413 ($M^+$, 60), 308 (100), 309 (35), 414 (19), 189 (85).

**1-(4-methoxyphenyl)-2,3,5-triphenyl-1H-pyrrole** (Table 6 entry 9)

Light yellow solid, MP = 139°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.94(d, *J* = 6.0 Hz, 1H), 7.45(m, 1H), 7.20-7.01 (m, 13H), 6.84 (t, *J* = 7.5 Hz, 2H), 6.65 (s, 2H), 6.62 (s, 1H), 3.69 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 159.25, 136.16, 134.86, 132.70, 132.44, 131.45, 129.96, 129.66, 129.49, 129.12, 129.09, 127.94, 127.82, 127.14, 126.84, 126.22, 125.38, 123.21, 113.60, 109.61, 55.23; **MS**-$C_{23}H_{29}NO$ (401) m/z (%): 401($M^+$, 100), 402 (31), 403 (5), 386 (4), 400 (4).

**4,5-dimethyl-2-(2,3,5-triphenyl-1H-pyrrol-1-yl)aniline** (Table 6 entry 10)

Clear oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.15-7.10 (m, 10H), 6.69 (s, 1H), 6.49 (s, 1H), 6.37 (s, 2H), 3.24 (s, br, 2H), 2.09 (s, 3H), 1.96 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 141.26, 137.68, 135.68, 133.07, 130.58, 127.94, 127.89, 126.59, 126.18, 122.68, 117.42, 109.83, 19.68, 18.71; **MS**-$C_{30}H_{26}N_2$ (414) m/z (%): 414 ($M^+$, 100), 310 (34), 415 (32), 337 (19), 413 (18).

**1-(3-phenylpropyl)-2,5-di(thiophen-2-yl)-1H-pyrrole** (Table 6 entry 11)

Brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.21-6.85 (m, 11H), 6.25 (s, 2H), 4.07 (t, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.80 (quin, *J* = 7.5 Hz, 2H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 140.81, 134.77, 128.35, 128.29, 128.19, 127.28, 125.88, 125.86, 125.20, 110.81, 44.62, 32.65, 32.36; **MS**-$C_{21}H_{19}NS_2$ (349) m/z (%): 349 ($M^+$, 100), 245 (40), 230 (32), 244 (31), 91 (28).

**1-(4-methoxyphenyl)-2,5-di(thiophen-2-yl)-1H-pyrrole** (Table 6 entry 12)

Pale green solid, MP = 183°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.18-7.13 (m, 2H), 6.98 (d, *J* = 3.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.74 (t, *J* = 7.5 Hz, 2H), 6.50 (d, *J* = 3.0 Hz, 2H), 3.80 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 159.99, 135.05, 131.03, 130.99, 130.33, 126.86, 123.94, 123.81, 114.30, 109.37, 55.45; **MS**-$C_{19}H_{15}NOS_2$ (337) m/z (%): 337 ($M^+$, 100), 338 (24), 339 (12), 322 (10), 213 (8).

**2-(2,5-di(thiophen-2-yl)-1H-pyrrol-1-yl)-4,5-dimethylaniline** (Table 6 entry 13)

Yellow solid, MP = 127°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 6.95(t, *J* = 3.0 Hz, 2H), 6.85 (s, 1H), 6.78-6.65 (m, 5H), 6.54 (s, 2H), 3.30 (s, br, 2H), 2.20 (s, 3H), 2.08 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 142.65, 139.47, 134.62, 131.12, 129.58, 127.11, 126.99, 123.47, 122.90, 121.32, 117.61, 109.43, 19.93, 18.74; **MS**-$C_{20}H_{18}N_2S_2$ (350) m/z (%): 350 ($M^+$, 100), 351 (31), 240 (27), 317 (20), 241 (10).

***tert*-butyl (4-(2,5-dimethyl-1H-pyrrol-1-yl)benzyl)-carbamate** (Table 7 entry 1)

Dark orange oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.31 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 5.84 (s, 2H), 5.01 (s, br, 1H), 4.32 (s, 2H), 1.96 (s, 6H), 1.43 (s, 9H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 155.87, 138.41, 137.82, 128.64, 128.18, 127.84, 105.54, 79.54, 44.00, 28.30, 12.93; **MS**-$C_{18}H_{24}N_2O_2$ (300) m/z (%): 300 ($M^+$, 85), 244 (100), 200 (86), 199 (78), 184 (35).

***tert-butyl* (4-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-carbamate** (Table 7 entry 2)

Off-white solid, MP = 175°C ; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.38 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.66 (s, br, 1H), 5.83 (s, 2H), 1.95 (s, 6H), 1.49 (s, 9H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 152.94, 138.01, 133.86, 129.10, 128.90, 119.02, 105.61, 81.05, 28.51, 13.17; **MS**-$C_{17}H_{22}N_2O_2$ (286) m/z (%): 286 ($M^+$, 28), 186 (100), 185 (63), 230 (53), 130 (34).

***tert-butyl* (6-(2,5-dimethyl-1H-pyrrol-1-yl)hexyl)carbamate** (Table 7 entry 3)

Brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 5.56 (s, 2H), 4.51 (s, br, 1H), 3.53 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.03 (s, 6H), 1.43-1.38 (m, 2H), 1.24 (s, 9H), 1.25-1.17(m, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 155.66, 126.91, 104.54, 78.59, 45.57, 43.17, 30.58, 28.08, 26.28, 26.16, 12.17, 8.38; **MS**-$C_{17}H_{30}N_2O_2$ (294) m/z (%): 294 ($M^+$, 72), 108 (100), 109 (85), 237 (67), 221 (45).

**5-(benzyloxy)-3-(2-(2,5-dimethyl-1H-pyrrol-1-yl)ethyl)-1H-indole** (Table 7 entry 4)

Brown oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.98 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.43-7.31 (m, 3H), 7.21 (d, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 12.0 Hz, 2H), 6.82 (s, 1H), 5.83 (s, 2H), 5.13 (s, 2H), 3.98 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.18 (s, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 153.34,

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137.89, 131.77, 128.82, 128.09, 127.87, 127.81, 127.76, 123.22, 113.21, 112.63, 112.24, 105.41, 102.21, 71.13, 44.60, 27.19, 12.76; **MS**-$C_{23}H_{24}N_2O$ (344) m/z (%): 344 ($M^+$, 75), 236 (100), 253 (48), 91 (31), 108 (28).

***tert*-butyl (4-(2-methyl-5-phenyl-1H-pyrrol-1-yl)benzyl)-carbamate** (Table 7 entry 5)

Off-white solid, MP = 125°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.17 (d, *J* = 9.0 Hz, 2H), 7.04-6.95 (m, 7H), 6.26 (d, *J* = 7.5 Hz, 1H), 6.01 (d, *J* = 7.5 Hz, 1H), 4.86 (s, br, 1H), 4.26 (s, 2H), 2.04 (s, 3H), 1.39 (s, 9H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 155.86, 138.30, 138.08, 134.07, 133.37, 131.65, 128.41, 127.90, 127.75, 127.69, 125.61, 108.65, 107.48, 79.63, 44.03, 28.34, 13.30; **MS**-$C_{23}H_{26}N_2O_2$ (362) m/z (%): 362 ($M^+$, 1), 262 (100), 207 (35), 261 (25), 263 (21).

***tert*-butyl (4-(2-methyl-5-phenyl-1H-pyrrol-1-yl)phenyl)-carbamate** (Table 7 entry 6)

Off-white solid, MP = 173°C; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.31 (d, *J* = 6.0 Hz, 2H), 7.09-7.00 (m, 7H), 6.63 (s, br, 1H), 6.31 (d, *J* = 3.0 Hz, 1H), 6.05 (d, *J* = 3.0 Hz, 1H), 2.07 (s, 3H), 1.49 (s, 9H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 152.85, 137.80, 134.26, 133.66, 132.04, 129.11, 128.18, 127.93, 125.84, 118.75, 108.67, 107.54, 81.02, 28.53, 13.51; **MS**-$C_{22}H_{24}N_2O_2$ (348) m/z (%): 348 ($M^+$, 1), 248 (100), 207 (27), 206 (24), 247 (20).

***tert*-butyl (6-(2-methyl-5-phenyl-1H-pyrrol-1-yl)hexyl)-carbamate** (Table 7 entry 7)

Yellow oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.34-7.22 (m, 5h), 6.02 (d, *J* = 4.5 Hz, 1H), 5.89 (d, *J* = 4.5 Hz, 1H), 4.40 (s, br, 1H), 3.79 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.24 (s, 3H), 1.46-1.33 (m, 2H), 1.29 (s, 9H), 1.27-1.20(m, 6H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 134.33, 133.75, 129.61, 128.91, 128.25, 126.55, 118.68, 107.70, 106.64, 78.98, 43.81, 40.29, 30.79, 29.76, 28.36, 26.14, 26.11, 12.68; **MS**-$C_{22}H_{32}N_2O_2$ (356) m/z (%): 356 ($M^+$, 55), 170 (100), 156 (31), 299 (30), 171 (27).

**5-(benzyloxy)-3-(2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)ethyl)-1H-indole** (Table 7 entry 8)

Greenish oil; **$^1$H NMR** (300.128 MHz, $CDCl_3$), δ (ppm) 7.78 (s, br, 1H), 7.46-7.13 (m, 10H), 6.86 (dd, *J* = 4.5 Hz, 1H), 6.71-6.68 (m, 3H), 6.09 (d, *J* = 3.0 Hz, 1H), 5.95 (d, *J* = 3.0 Hz, 1H), 4.96 (s, 2H), 4.10 (t, *J* = 7.5 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 3H); **$^{13}$C NMR** (75.474 MHz, $CDCl_3$), δ (ppm) 153.09, 137.54, 134.31, 133.71, 131.37, 129.68, 129.07, 128.54, 128.49, 128.28, 127.79, 127.59, 126.72, 122.67, 112.97, 112.23, 111.76, 107.96, 106.72, 101.76, 70.92, 44.80, 27.04, 12.70; **MS**-$C_{28}H_{26}N_2O$ (406) m/z (%): 406 ($M^+$, 100), 236 (96), 315 (53), 91 (40), 170 (36).

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