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Graphical Abstract

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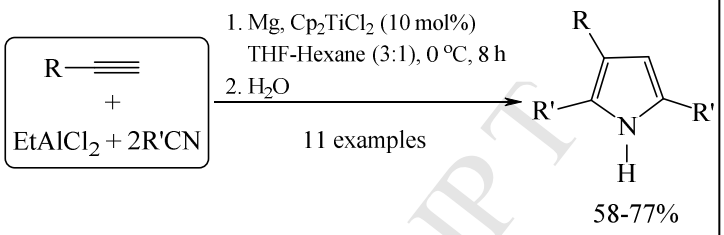

One-pot synthesis of 2,3,5-substituted 1*H*-pyrroles via the reaction of terminal acetylenes with nitriles and $EtAlCl_2$ catalyzed by Cp_2TiCl_2

Leila O. Khafizova,* Mariya G. Shaibakova, Nikita A. Rikhter, Tatyana V. Tyumkina, Usein M. Dzhemilev

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Abstract

A new one pot method for the synthesis of 2,3,5-substituted 1*H*-pyrroles in moderate to good yields (58-77%) based on multicomponent reaction of terminal acetylenes with nitriles and $EtAlCl_2$ in the presence of Cp_2TiCl_2 catalyst and metallic magnesium has been developed. The possible mechanistic pathway to substituted pyrroles is discussed.

Keywords: Titanium catalysis, Terminal acetylenes, Nitriles, Ethylaluminum dichloride, 2,3,5-Substituted 1*H*-pyrroles

1. Introduction

The pyrrole ring is part of many important biologically active natural products such as hemoglobin, chlorophyll, bile pigments, and vitamin B12, that participate in the processes of oxygen transfer in living organisms, fixation of solar energy in plants, oxygen transport processes and other life-supporting reactions.[1] It is also one of the structural units of the most important drugs, having anticancer, antitumor, and antibacterial ~~diseases~~ properties.[2] Several pyrrole derivatives are cholesterol lowering agents (atorvastatin or ~~lipitor~~ Lipitor®)[3a] and HIV fusion inhibitors.[3b] Pyrrole derivatives are also applied for the preparation of semiconducting and fluorescence materials.[4]

In the literature, there is a sufficiently large number of publications concerning the synthesis and study of the properties of pyrroles and ~~its~~ their derivatives. Traditional methods for the pyrrole synthesis include thermal transformations of enolized ketazines in the presence of Lewis acids (*Piloty-Robinson reaction*),[5] condensation of 1,4-dicarbonyl compounds with primary amines (*Paal−Knorr reaction*),[6] as well as multicomponent condensation of aldehydes

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with β-ketoesters in the presence of ammonia (*Hantzsch reaction*)[7]. It should be noted that, along with the procedures listed, in the literature,[8] various modifications of these methods are presented.

Despite numerous publications devoted to various aspects of the synthesis and use of pyrroles, interest in these studies is not weakened, and the development of efficient methods for the synthesis of practically important pyrroles based on the use of available starting reagents and catalysts is one of the important and promising directions of research.

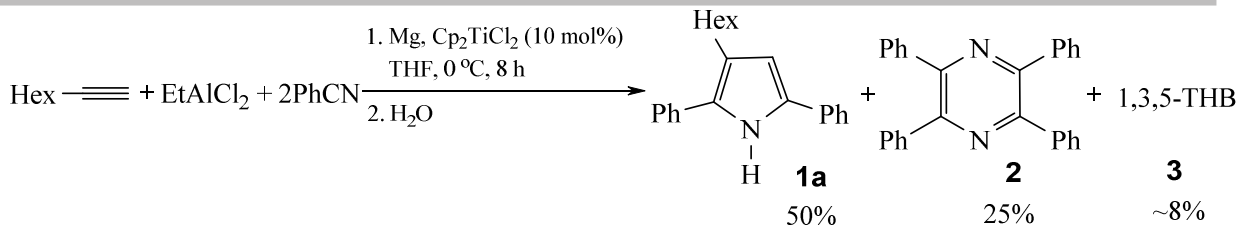
Methods for the preparation of pyrroles using zirconium and titanium-containing reagents are also known.[9] Titanium-mediated reactions have been shown to be highly efficient for the formation of carbon-carbon or carbon-heteroatom bonds, and therefore titanocycles are important intermediates for further selective transformations.

Here, we report the one-pot and efficient synthesis of 2,3,5-substituted 1*H*-pyrroles via a multicomponent reaction between terminal acetylenes and organic nitriles in the presence of $EtAlCl_2$, metallic Mg and the Cp_2TiCl_2 catalyst in moderate to good yields (58-77%).

2. Results and Discussion

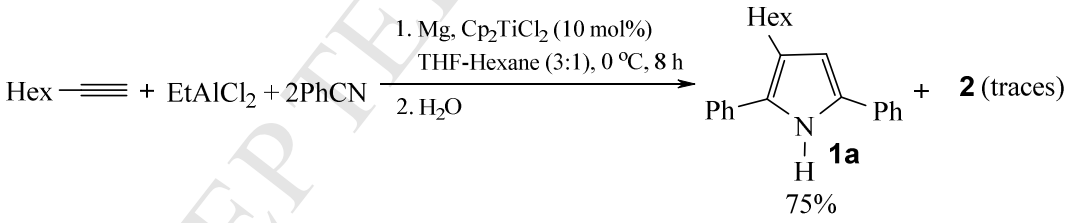
Recently, we have shown that the reaction between substituted acetylenes, $EtAlCl_2$, and carboxylic acid esters in the presence of metallic Mg and the Cp_2TiCl_2 catalyst leads to the formation of tetrasubstituted furans.[9~~10~~] In continuation of this research, as well as to investigate into the possibilities of the above reaction, we have studied the reaction between terminal acetylenes, $EtAlCl_2$ and organic nitriles under Cp_2TiCl_2 catalysis.

Preliminary experiments have shown that the model reaction of oct-1-yne with $EtAlCl_2$ and benzonitrile in the presence of metallic Mg (~~chloride ion acceptor~~ a reducing agent) and the Cp_2TiCl_2 catalyst under reaction conditions (oct-1-yne : [Al] : benzonitrile : Mg : [Ti] = 1 : 4 : 2 : 4 : 0.1, THF, 0 ^oC, 8 h) affords 3-hexyl-2,5-diphenyl-1*H*-pyrrole **1a** in 50% yield (based on the initial benzonitrile) after alkaline hydrolysis of the reaction mixture (Scheme 1). Along with **1a**, we have identified tetraphenylpyrazine **2** (25%), which is formed as a result of the competing reaction between benzonitrile and $EtAlCl_2$ under Cp_2TiCl_2 catalysis.[~~10~~11] Together with **1a** and **2**, small amounts of 1,3,5-trihexylbenzene (1,3,5-THB) **3** were formed in the yield that did not exceed 8% (based on the initial acetylene).



Scheme 1. Reaction of oct-1-yne with benzonitrile and $EtAlCl_2$ catalyzed by Cp_2TiCl_2 in tetrahydrofuran

To improve the selectivity of the above reaction, we have estimated the effect of the solvent nature, catalyst concentration, and temperature of the reaction on the yield and content of the products formed in the reaction. It is interesting to note that the use of a mixture of solvents (tetrahydrofuran-hexane) allowed increasing the yield of 3-hexyl-2,5-diphenyl-1*H*-pyrrole **1a.** Thus, in a 3:1 mixture of THF/hexane, the yield of **1a** increased to 75%, and tetraphenylpyrazine **2** was detected only in trace amounts (Scheme 2). The amount of the catalyst has a significant effect on the yield of pyrrole **1a**. Thus, the highest yield of **1a** occurred at Cp_2TiCl_2 concentration of 10 mol% at ~ 0 °C. As the catalyst concentration decreases to 1 mol%, the yield of **1a** is reduced to 10%, which is probably due to a decrease in the concentration of catalytically active centres in the reaction mass. With increase in catalyst concentration (more than 10 mol%), the yield of the main reaction product remained unchanged.



	C, mol%	yield of **1a**, %
Cp_2TiCl_2 catalyst	1	10
	10	75
	> 10	no change

Scheme 2. Reaction of oct-1-yne with benzonitrile and $EtAlCl_2$ catalyzed by Cp_2TiCl_2 in a mixture of THF-hexane (3:1)

The structure of the resulting 3-hexyl-2,5-diphenyl-1*H*-pyrrole **1a** was determined using spectroscopic analysis (^{13}C and ^{1}H NMR, IR) and mass spectrometry. In the ^{13}C NMR spectrum, the signals, assigned to the carbon atoms of the trisubstituted pyrrole ring, appear at 123.8, 129.3,

108.3 and 131.5 ppm for the C(2), C (3), C(4), and C(5) atoms, respectively. The assignments were made on the basis of homonuclear (COSY) and heteronuclear correlation (HSQC, HMBC) experiments. Thus, based on the literature data,[11,12] the signal at δc 108.3 ppm was attributed to the *β*-unsaturated carbon atom in the nitrogen-containing heterocyclic skeleton. The HSQC spectrum demonstrates that there exists the correlation between this signal and the doublet at 6.5 ppm attributed to pyrrole ring proton. The spin-spin coupling constant, equal to 4.0 Hz, indicates the existence of a long-range interaction with proton at the nitrogen atom, which is characteristic for strongly bound states of aromatic systems. The long-range spin-spin coupling constant is also observed in the COSY spectrum. Reliable signal assignments for C(3) and C(5) carbon atoms were performed from the HMBC experiment, since the HMBC spectra contain cross peaks between hydrogen and carbon atoms for H(4) − (3), H(4) − C (5), H(1') – C(2) and H(1') – C(4).

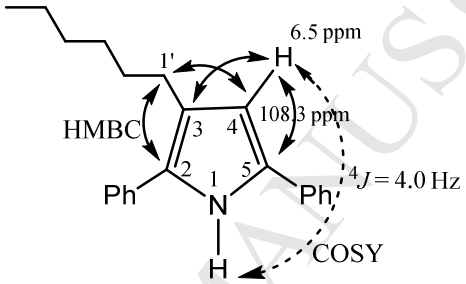
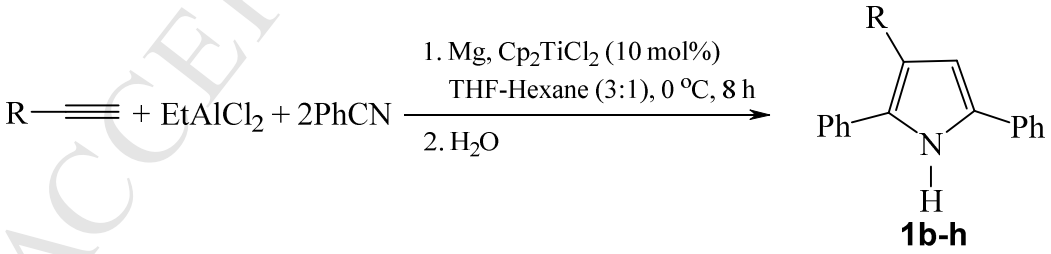


Fig. 1. Main COSY, HMBC correlation for **1a**.

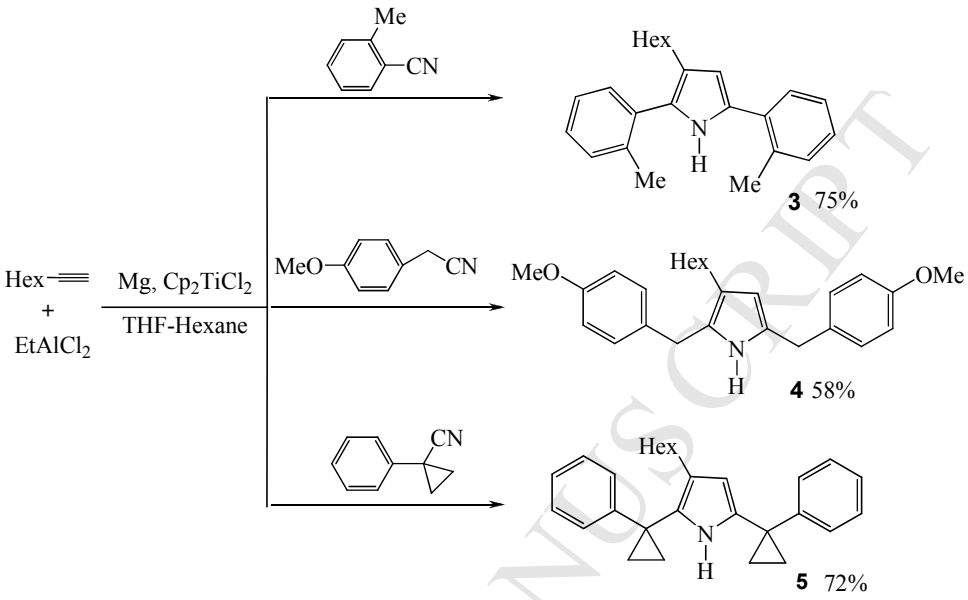
In analogous fashion, other terminal acetylenes (hex-1-yne, hept-1-yne, dec-1-yne, phenylacetylene, but-3-yn-1-yl-benzene), as well as cyclopropylacetylene and cyclopentylacetylene react with $EtAlCl_2$ and benzonitrile in the presence of metallic Mg and the Cp_2TiCl_2 catalyst (THF-hexane (3:1), 0 ^oC) to afford the corresponding 2,3,5-substituted pyrroles **1b-h** in 67-77% yield (Scheme 3).



R = b: Bu (74%), c: Pent (77%), d: Oct (72%), e: cyclo-Pr (74%), f: cyclo-Pent (76%), g: Ph (76%), h: $(CH_2)_2Ph$ (67%)

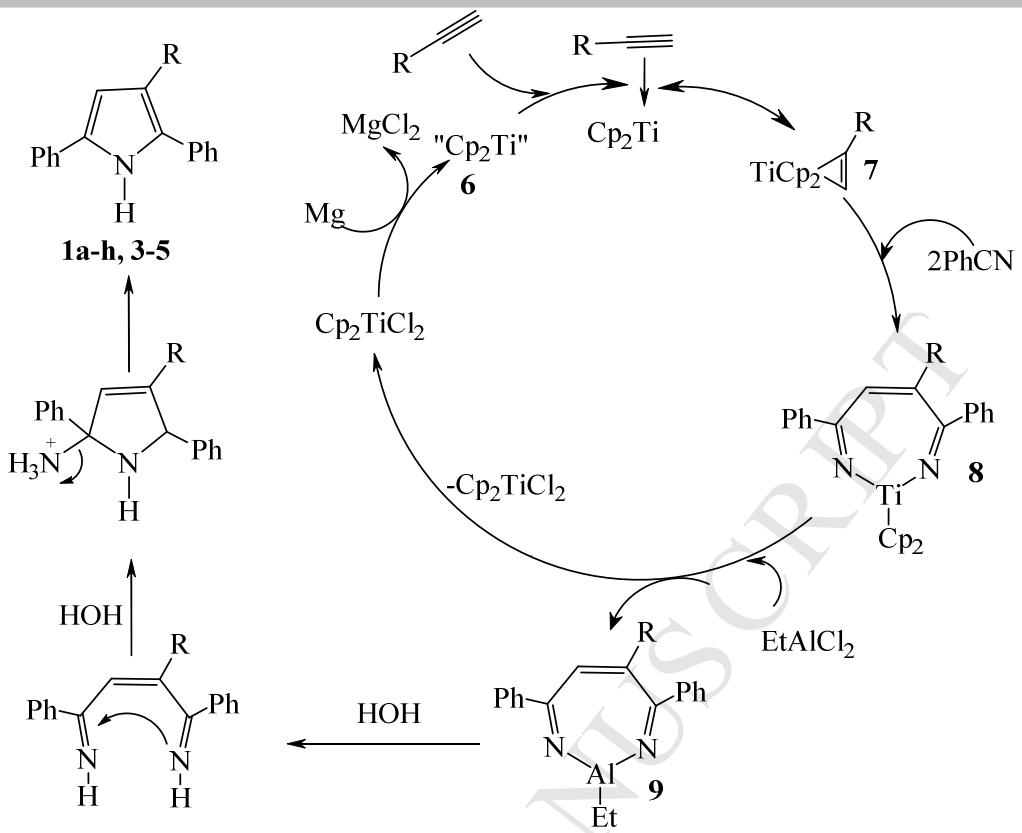
Scheme 3. Synthesis of 2,3,5-substituted 1*H*-pyrroles by the reaction of terminal acetylenes with benzonitrile and $EtAlCl_2$ catalyzed by Cp_2TiCl_2.

~~The reaction is of a general nature, since~~, Other nitriles, for example, 2-methylbenzonitrile, 4-methoxyphenylacetonitrile or 1-phenylcyclopropanecarbonitrile also give 2,3,5-substituted pyrroles **3-5** (Scheme 4).



Scheme 4. Synthesis of 2,3,5-substituted 1*H*-pyrroles by the reaction of oct-1-yne with aromatic nitriles and $EtAlCl_2$ catalyzed by Cp_2TiCl_2.

On the basis of the data available in the literature, as well as our own experimental results, we assume that the sequence of transformations to give substituted pyrroles (**1a-h, 3-5**) in the reaction between terminal acetylenes, benzonitrile and $EtAlCl_2$ catalyzed by Cp_2TiCl_2 initially includes the formation of titanocene "Cp_2Ti" **6** from Cp_2TiCl_2 and titanacyclopropene intermediate **7**.[~~12~~13] The subsequent insertion of two molecules of the original nitrile into the active Ti-C bonds in complex **7** yields diaminotitanacycloheptatriene **8**. Transmetallation of the intermediate **8** with $EtAlCl_2$ results in diaminoaluminacycloheptatriene **9** with simultaneous regeneration of the original catalyst Cp_2TiCl_2. Finally, hydrolysis and subsequent intramolecular rearrangement of intermediate **9** lead to 2,3,5-substituted 1*H*-pyrroles **1a-h, 3-5** (Scheme 5).



Scheme 5. Possible pathway for the formation of 2,3,5-substituted 1*H*-pyrroles from terminal acetylenes, nitriles and ethylaluminum dichloride in the presence of the Cp_2TiCl_2 catalyst.

3. Conclusion

Thus, we have developed a new efficient one-pot method for the synthesis of 2,3,5-substituted 1*H*-pyrroles in moderate to good yields (58-77%). This approach allows producing hard accessible and significant five-membered heterocycles in one preparative stage under optimized reaction conditions (0 ^{o}C, THF-hexane (3:1)) from terminal acetylenes and organic nitriles in the presence of $EtAlCl_2$ and the Cp_2TiCl_2 catalyst. Since the starting materials and reagents required for this reaction are commercially available, the present synthesis is preferable from a practical point of view. Further investigations into preparation of new heterocyclic compounds using the developed method are currently in progress.

4. Experimental

4.1. General

Chromatographic analysis was performed on a Shimadzu GC-9A instrument using a 2000×2 mm column, the SE-30 (5 %) stationary phase on Chromaton N-AW-HMDS (0.125-0.160 mm),

helium carrier gas (30 mL/min), temperature programming from 50 to 300 ^{o}C at a 8 ^{o}C/min rate. The ^{1}H and ^{13}C ~~^{31}P~~ NMR spectra were measured in $CDCl_3$ on a Bruker Avance-400 spectrometer (100.62 MHz for ^{13}C, 400.00 MHz for ^{1}H). Elemental analysis (C, H) of the samples was performed using an elemental analyzer (KCarlo Erba, model 1106). The mass spectra were recorded on a Finnigan 4021 instrument (HP-5 glass capillary column, 50 000 x 0.25 mm; carrier gas helium; oven temperature programming from 50 to 300 °C at a rate of 5 deg/min, evaporator temperature 280 °C, the temperature of the ion source 250 °C [EI, 70 eV]). TLC was performed on Silufol UV-254 plates with hexane–ethyl acetate (100:3-10) mixture as the eluent and I_2 for visualization. For column chromatography, Acros silica gel (0.060–0.200 mm) was used. Reactions with organometallic compounds were performed in a dry argon flow. The solvents were dried and distilled immediately prior to use. Commercially available terminal acetylenes, Cp_2TiCl_2 and Et_2AlCl_2 (Aldrich) were used.

4.2.Reaction of terminal acetylenes with nitriles and $EtAlCl_2$ catalyzed by Cp_2TiCl_2 (general procedure)

A 100 mL glass reactor equipped with a magnetic stirrer under a dry argon atmosphere at 0 $^{\circ}$C, was charged under stirring with THF (45 mL), $EtAlCl_2$ (5,6 mL, 40 mmol), Mg (0,96 g, 40 mmol, powdered) and the Cp_2TiCl_2 catalyst (0,248 g, 1.0 mmol). After 1 h, hexane (15 mL), acetylene (5 10 mmol) and nitrile (10 20 mmol) were added. The mixture was stirred for additional 7 h. After the addition of Et_2O (15 mL), the mixture was treated with 0.1 M aq NaOH (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). Combined organic layers were dried over $MgSO_4$. Solvent was evaporated and the residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent.

4.2.1. 3-Hexyl-2,5-diphenyl-1H-pyrrole (1a)

R_f 0.56, (hexane~~s~~/EtOAc = 100:3), yellow oil (yield 75 %, 1136 mg). IR (neat): 3442, 3059, 2954, 2925, 2856, 1606, 1519, 1456, 1265, 758, 695cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 8 Hz, 3H, CH_3), 1.33-1.42 (m, 6H, CH_2), 1.69 (~~pent~~ guint, J = 8 Hz, 2H, CH_2), 2.67 (t, J = 8 Hz, 2H, CH_2), 6.52 (d, J = 4 Hz, 1H, CH), 7.23-7.54 (m, 10H, $CH_{(Ar)}$), 8.28 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.11, 22.67, 26.58, 29.37, 31.11, 31.78, 108.33, 123.61, 123.77, 126.11, 126.33, 126.77, 128.77, 128.89, 129.31, 131.54, 132.57, 133.56. MS, *m/z*: 303 (M^+). Anal. Calcd for $C_{22}H_{25}N$: C 87.08, H 8.30, N 4.62. Found: C 87.03, H 8.21.

4.2.2. 3-Butyl-2,5-diphenyl-1H-pyrrole (1b).

R_f 0.45, (hexanes/EtOAc = 100:4), yellow oil (yield 74%, 1017 mg). IR (neat): 3442, 3059, 2955, 2927, 2857, 1606, 1493, 1455, 1264, 1073, 757, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 8Hz, 3H, CH_3), 1.42-1.47 (m, 2H, CH_2), 1.68 (~~pent~~ guint, J = 8 Hz, 2H, CH_2), 2.68 (t, 2H, J = 8 Hz, 2H, CH_2), 6.53 (s, 1H, CH), 7.23-7.54 (m, 10H, $CH_{(Ar)}$), 8.28 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.04, 22.74, 26.27, 33.34, 108.35, 123.60, 123.71, 126.12, 126.34, 126.77, 128.77, 128.89, 129.32, 131.54, 132.56, 133.56. MS, *m/z*: 275 (M^+). Anal. Calcd for $C_{20}H_{21.}N$: C 87.23, H 7.69, N 5.09. Found: C 87.12, H 7.77.

4.2.3. 3-Pentyl-2,5-diphenyl-1H-pyrrole (1c).

R_f 0.50, (hexanes/EtOAc = 100:3), slight yellow oil (yeild 77%, 1113 mg). IR (neat): 3441, 3060, 2954, 2926, 2856, 1670, 1606, 1493, 1455, 1262, 759, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 8Hz, 3H, CH_3), 1.28, (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 1.70 (~~pent~~ guint, J = 8 Hz, 2H, CH_2), 2.67 (t, J = 8 Hz, 2H, CH_2), 6.53 (s, 1H, CH), 7.23-7.54 (m, 10H, $CH_{(Ar)}$), 8.29 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.10, 22.61, 26.55, 30.83, 31.91, 108.33, 123.61, 123.75, 126.11, 126.33, 126.77, 128.76, 128.88, 129.53, 131.62, 132.56, 133.47. MS, *m/z*: 289 (M^+). Anal. Calcd for $C_{21}H_{23}N$: C 87.15, H 8.01, N 4.84. Found: C 87.04, H 7.89.

4.2.4. 3-Octyl-2,5-diphenyl-1H-pyrrole (1d).

R_f 0.55, (hexanes/EtOAc = 100:3), yellow oil (yield 72 %, 1191 mg). IR (neat): 3437, 3060, 2924, 2853, 1605, 1493, 1455, 1287, 759, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, 3H, CH_3), 1.24-1.42 (m, 10H, CH_2), 1.69 (m, 2H, CH_2), 2.68 (t, J = 8 Hz, 2H, CH_2), 6.53 (s, 1H, CH), 7.21-7.54 (m, 10H, $CH_{(Ar)}$), 8.29 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.13, 22.70, 26.58, 29.32, 29.53, 29.70, 31.15, 31.92, 108.34, 123.62, 123.77, 126.11, 126.33, 126.78, 128.77, 128.89, 129.32, 131.64, 132.58, 133.58. MS, *m/z*: 331 (M^+). Anal. Calcd for $C_{24}H_{29}N$: C 86.96, H 8.82, N 4.23. Found: C 86.72, H 8.39.

4.2.5. 3-Cyclopropyl-2,5-diphenyl-1H-pyrrole (1e).

R_f 0.55, (hexanes/EtOAc = 100:1), yellow oil (yield 74%, 958 mg). IR (neat): 3440, 3058, 2956, 2925, 2855, 1668, 1605, 1495, 1455, 1263, 760, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.70 (m, 2H, CH_2), 0.94 (m, 2H, CH_2), 1.99 (m, 1H, CH), 6.29 (s, 1H, CH), 7.23-7.67 (m, 10H, $CH_{(Ar)}$), 8.32 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 8.18, 8.24, 105.50, 123.66, 125.16, 126.24, 126.43, 126.75, 128.90, 130.22, 131.53, 132.46, 133.31. MS, *m/z*: 259 (M^+). Anal. Calcd for $C_{19}H_{17}N$: C 87.99, H 6.61, N 5.40. Found: C 87.85, H 6.50.

4.2.6. 3-Cyclopentyl-2,5-diphenyl-1H-pyrrole (1f).

R_f 0.50, (hexanes/EtOAc = 100:3), orange oil (yield 76%, 1091 mg). IR (neat): 3438, 3059, 2958, 2926, 2857, 1670, 1604, 1494, 1456, 1265, 758, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.65-1.75 (m, 4H, $C^{2,3,4,5}\underline{H^a}H^b$),* 1.82-1.90 (m, 2H, $C^{3,4}H^a\underline{H^b}$), 2.02-2.10 (m, 2H, $C^{2,5}H^a\underline{H^b}$), 3.15-3.22 (m, 1H, $C^1\underline{H}$), 6.57 (d, J = 4 Hz, 1H, CH), 7.22-7.54 (m, 10H, $CH_{(Ar)}$), 8.24 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 25.64, 35.41, 37.00, 105.74, 123.62, 126.12, 126.52, 127.34, 127.84, 128.74, 128.87, 129.55, 131.83, 132.52, 133.65. MS, *m/z*: 287 (M^+). Anal. Calcd for $C_{21}H_{21}N$: C 87.76, H 7.36, N 4.87. Found: C 87.55, H 7.30.

*Diastereaotopic protons of the cyclopentyl substituent are designated as H^a (which exhibit upfield signals) and H^b (which exhibit downfield signals). The numbering of carbons are given in *Supplementary materials*.

4.2.7. 3-Phenyl-2,5-diphenyl-1H-pyrrole (1g).

R_f 0.65, (hexanes/EtOAc = 100:5), white solid, mp 126–128 °C, (yield 76 %, 1121 mg). IR (neat): 3435, 3059, 3023, 2923, 2851, 1949, 1666, 1606, 1486, 1467, 1261, 1217, 1072, 955, 757, 696, 587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 1H, CH), 7.24-7.38 (m, 9H, $CH_{(Ar)}$), 7.42-7.46 (m, 4H, $CH_{(Ar)}$), 7.58-7.60 (m, 2H, $CH_{(Ar)}$), 8.48 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 108.61, 123.82, 124.03, 125.97, 126.55, 127.00, 127.52, 128.36, 128.44, 128.74, 129.01, 129.34, 132.25, 133.10, 134.92, 136.38. MS, *m/z*: 295 (M^+). Anal. Calcd for $C_{22}H_{17}N$: C 89.46, H 5.80, N 4.74. Found: C 89.23, H 5.67.

4.2.8. 2,5-Diphenyl-3-(2-phenylethyl)-1H-pyrrole (1h).

R_f 0.58, (hexanes/EtOAc = 100:4), yellow solid, mp 136 –137 °C, (yeild 67 %, 1082 mg). IR (neat): 3437, 3059, 3025, 2920, 2851, 1958, 1669, 1604, 1493, 1453, 1265, 1211, 1073, 907,804, 758, 696, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 4H, CH_2), 6.57 (d, J = 4 Hz, 1H, CH), 7.23-7.34 (m, 9H, $CH_{(Ar)}$), 7.39-7.45 (m, 4H, $CH_{(Ar)}$), 7.53-7.55 (m, 2H, $CH_{(Ar)}$), 8.32 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.77, 37.40, 108.21, 122.65, 123.66, 125.85, 126.23, 126.51, 126.83, 128.32, 128.49, 128.81, 128.94, 129.61, 131.66, 132.50, 133.35, 142.33. MS, *m/z*: 323 (M^+). Anal. Calcd for $C_{24}H_{21}N$: C 89.12, H 6.54, N 4.33. Found: C 89.01, H 6.39.

4.2.9. 2,3,5,6-Tetraphenylpyrazin (2).

R_f 0.54 (hexanes/EtOAc = 100:3), white solid, mp 247–248 °C,[10] (yeild 25 %, 240 mg). IR (neat): 3460, 3445, 3083, 3059 2850, 1958, 1600, 1493, 1454, 1404, 1218,1128, 1075, 1028, 733, 695, 598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, 12H, $CH_{(Ar)}$), 7.68-7.65 (m,

8H, $CH_{(Ar)}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ 128.23, 128.60, 129.89, 138.44, 148.42. MALDI TOF/ TOF, *m/z* 385.1707 $[M+H]^+$, Calcd for $C_{28}H_{21}N_2$ $[M+H]^+$ 385.1711.

4.2.10. 3-Hexyl-2,5-bis(2-methylphenyl)-1H-pyrrole (3).

R_f 0.55, (hexanes/EtOAc = 100:3), white oil (yield 75 %, 1241 mg). IR (neat): 3442, 2925, 2855, 1949, 1606, 1519, 1456, 1286, 805, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 8Hz, 3H, CH_3), 1.27-1.31 (m, 6H, CH_2), 1.58 (~~pent~~ guint, *J* = 8 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.42 (t, *J* = 8 Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 6.34 (d, *J* = 4 Hz, 1H CH), 7.18-7.42 (m, 8H, $CH_{(ar)}$), 7.95 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.10, 20.33, 21.60, 22.67, 26.20, 29.18, 31.11, 31.73, 109.74, 122.93, 125.57, 126.02, 126.09, 126.31, 127.35, 127.67, 128.29, 130.23, 130.29, 131.01, 131.18, 132.84, 133.23, 134.48, 137.47. MS, *m/z*: 331 (M^+). Anal. Calcd for $C_{24}H_{29}N$: C 86.96, H 8.82, N 4.23. Found: C 86.75, H 8.70.

4.2.11. 3-Hexyl-2,5-bis(4-methoxybenzyl)-1H-pyrrole (4).

R_f 0.42, (hexanes/EtOAc = 100:10), yellow oil (yield 58 %, 1134 mg). IR (neat): 3440, 2922, 2855, 2830, 1950, 1612, 1520, 1455, 1284, 804, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 8Hz, 3H, CH_3), 1.33-1.42 (m, 6H, CH_2), 1.69 (~~pent~~ guint, *J* = 8 Hz, 2H, CH_2), 2.67 (t, *J* = 8 Hz, 2H, CH_2), 3.62 (s, 4H, CH_2Ph), 3.82 (s, ~~3~~6H, CH_3), 6.52 (d, *J* = 4 Hz, 1H, CH), 6.88 (m, 4H, $CH_{(ar)}$), 7.11 (m, 4H, $CH_{(ar)}$), 7.28 (1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.51, 22.67, 26.68, 29.37, 31.11, 31.82, 33.45, 55.75, 114.29, 126.35, 131.07, 132.36, 138.74, 143.90, 146.82, 159.76. MS, *m/z*: 391 (M^+). Anal. Calcd for $C_{26}H_{33}NO_2$: C 79.76, H 8.50, O 8.17, N 3.58. Found: C 79.57, H 8.37.

4.2.12. 3-Hexyl-2,5-bis(1-phenylcyclopropyl)-1H-pyrrole (5).

R_f 0.60, (hexanes/EtOAc = 100:2), yellow oil (yield 72 %, 1379 mg). IR (neat): 3460, 3443, 3084, 3059, 3007, 2955, 2927, 2855, 1682, 16060, 1495, 1462, 1379, 1261, 1026, 799, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 8Hz, 3H, CH_3), 1.23-1.30 (m, 14H, CH_2 ($4CH_{2\ cyclopropyl}$, $3CH_{2\ alkyl}$)), 1.49 (~~pent~~ guint, *J* = 8 Hz, 2H, CH_2), 2.41 (t, *J* = 8 Hz, 2H, CH_2), 5.77 (d, *J* = 4Hz, 1H, CH), 7.10-7.51 (m, 10H, $CH_{(ar)}$), 7.99 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.10, 16.68, 17.43, 21.03, 22.64, 23.59, 26.04, 29.53, 30.60, 31.77, 104.99, 122.38, 125.13, 125.25, 126.13, 127.91, 128.09, 128.37, 130.89, 134.03, 144.52, 146.07. MS, *m/z*: 383 (M^+). Anal. Calcd for $C_{28}H_{33}N$: C 87.68, H 8.67, N 3.65. Found: C 87.50, H 8.58.

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