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Efficient Preparation of [1-^{15}N]-3-Cyano-4-methyl-1*H*-pyrrole by a Wittig-Based Strategy

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3-Cyano-4-methyl-1*H*-pyrrole (**1**) was prepared by a new Wittig procedure from simple, commercially available starting materials in four steps with an overall yield of 39 %. Similarly, [1-^{15}N]-3-cyano-4-methyl-1*H*-pyrrole (**1a**) was prepared starting from [^{15}N]-phthalimide. In this synthesis, Wittig coupling was used to form the central C–C bond of intermediate **6**, which has nitrile and methyl substituents. Upon deprotection and cyclization pyrrole **1** is obtained directly in one pot. This scheme also allows stable isotope incorporation at any position or a combination of positions. 3-Cyano-4-methyl-1*H*-pyrrole was converted into the novel 1-benzyl-3-cyano-4-methylpyrrole and the novel 4-methyl-1*H*-pyrrole-3-aldehyde. It is clear that this novel Wittig procedure has a wide scope that will allow the easy preparation of many new pyrrole systems.

Introduction

The substituted pyrrole ring is the basic building block in a number of important biological compounds, including vitamin B_{12}, chlorophyll, haem, etc.[1,2] Many pyrroles have important biological and pharmaceutical properties.[3]

Access to site-directed stable-isotope-enriched (^{13}C and ^{15}N) sites in these molecules will allow these compounds to be investigated through the use of isotope-sensitive techniques and without perturbation at the atomic level to determine the role that these systems play in biological fields. Only very few ^{15}N- and ^{13}C-enriched pyrroles are known that have isotope incorporation at only one position.[4] [1-^{15}N]-3-Cyano-4-methylpyrrole is the target of our efforts to find a simple synthetic scheme that allows this system to be prepared with a stable isotope label at any position or a combination of positions up to the uniformly isotope-labeled form.

We have chosen [1-^{15}N]-3-cyano-4-methylpyrrole as a 3,4-disubstituted pyrrole with two different substituents at the 3,4-positions, because these systems are not easily accessible with known synthetic procedures. They are also essential building blocks to prepare biologically important protoporphyrins, chlorophyll, and vitamin B_{12}. We have first pioneered a synthetic scheme to obtain 3-cyano-4-methylpyrrole with natural abundance starting materials that are also commercially available in the various stable isotope-enriched forms or can be prepared in stable isotope-enriched forms by simple synthetic procedures. The study is completed by preparing [1-^{15}N]-3-cyano-4-methylpyrrole starting from the commercially available [^{15}N]-phthalimide, and the target molecule was fully characterized spectroscopically.

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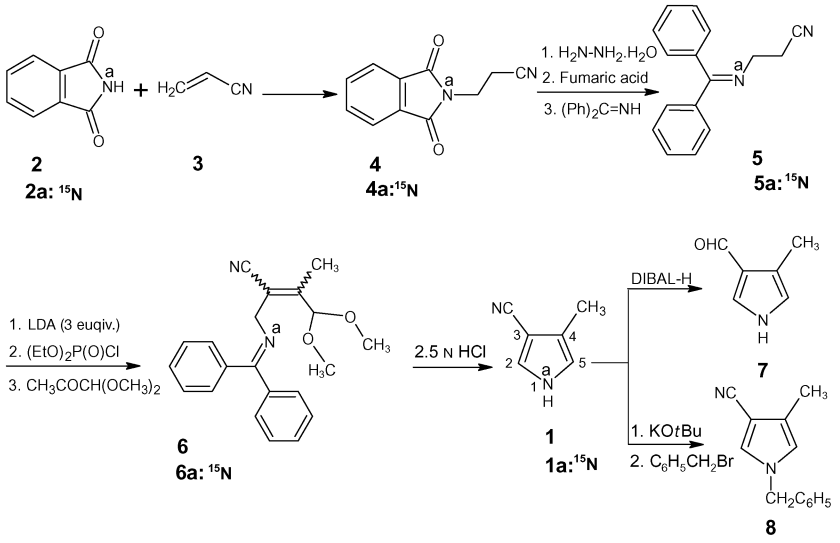
Results and Discussion

Synthesis

The conversions in Scheme 1 were first optimized through reactions with molecules in nonisotopically enriched forms. The strategy depicted in Scheme 1 starts with β-phthalimidopropionitrile (**4**; 4.05 g, 20 mmol), which can be prepared efficiently by the Michael addition of phthalimide (**2**; 3.0 g, 20 mmol) to acrylonitrile (**3**; 10 mL) in the presence of potassium phthalimide (0.3 g, 1.6 mmol).[5] Treatment of product **4** in ethanol with hydrazine hydrate yielded 3-aminopropionitrile in ethanol solution and 2,3-dihydrophthalazine-1,4-dione as a solid product, which was separated by simple filtration. The fumaric acid (ethanol solution) was added to the solution of 3-aminopropionitrile to obtain 3-aminopropionitrile fumarate (2.30 g, 18 mmol). The fumarate product was further treated with benzophenone imine (3.30 g, 18 mmol) to obtain 3-[(diphenylmethylene)amino]propionitrile (**5**; 3.51 g, 15 mmol) as a light-yellow crystalline product by a known procedure.[6]

Treatment of **5** (3.51 g, 15 mmol) with lithium diisopropylamide (LDA, 3 equiv.) in THF at –70 °C followed by the addition of diethyl chlorophosphate (2.58 g, 15 mmol) and subsequently 1,1-dimethoxyacetone (1.90 g, 16 mmol) whilst stirring resulted in an *E*/*Z* mixture of 2-{[(diphenylmethylene)amino]methyl}-4,4-dimethoxy-3-methylbut-2-enenitrile (**6**) in a 3:2 ratio. The *E*/*Z* mixture of **6**



Scheme 1. Preparation of 3-cyano-4-methyl-1*H*-pyrrole (**1**) and [1-^{15}N]-3-cyano-4-methyl-1*H*-pyrrole (**1a**) starting from phthalimide (**2**) and [^{15}N]-phthalimide (**2a**), respectively.

was purified by column chromatography on silica gel 60 with ethyl acetate/hexane (1:3) as eluent. The signals of the methyl group and methylene group in minor compound **6** showed an NOE interaction in the ^{1}H NMR spectra, which establishes this compound as the (*Z*)-**6** isomer and thus the major as the (*E*)-**6** isomer. Product **6** (4.35 g, 13 mmol) was stirred in 2.5 N HCl (50 mL) for 1 h at room temperature and further work up gave a mixture of 3-cyano-4-methyl-1*H*-pyrrole (**1**) and benzophenone. Column chromatography on silica gel 60 with ethyl acetate/hexane (1:3) gave **1** (0.89 g) in 65% yield. The R_f values of **1** and benzophenone are 0.22 and 0.45, respectively, in ethyl acetate/*n*-hexane (1:3). Our target molecule is now accessible from simple commercially available reagents in 39% overall yield based on the starting material **2**. All analytical data of **1** are in full agreement with those in the literature.[7,8] Repeating this reaction with commercial [^{15}N]-phthalimide gave [1-^{15}N]-3-cyano-4-methyl-1*H*-pyrrole (**1a**) in 36% overall yield. The *m*/*z* value of **1a** is 107.0505, which agrees very well with calculated value of 107.05309 for the formula $^{12}C_6{}^1H_6{}^{14}N^{15}N$.

The ^{1}H NMR chemical shifts of **1a** were compared with natural abundance chemical shifts of **1**. We observed a characteristic splitting of 97 Hz of NH (δ = 9 ppm) due to the presence of ^{15}N of pyrrole **1a**. Within experimental error, no signal due to ^{14}N incorporation is observed. This result is in agreement with the high (98%) ^{15}N incorporation of the ^{15}N labeled reagent, which showed that during the reaction no isotope dilution had taken place. The chemical shift of ^{15}NH of pyrrole **1a** is observed at δ = 153 ppm (compared to the ^{15}N signal of ammonium nitrate solution). This value compares well with the reported ^{15}N shift value of natural abundance pyrrole.[9]

All the reagents except 1,1-dimethoxyacetone used in Scheme 1 are commercially available in any stable isotope-enriched form. However, we prepared 1-chloroacetone in any isotopically labeled form,[10] which can be converted into the corresponding 2-oxopropan-1-al.[11]

Discussion

In Scheme 1, we used the Wittig reaction to couple two components in one step so that they form the 3–4 C–C bond of target molecule **1**. Intermediate **6** has substituents in the 1,5-positions. The deprotection and cyclization in acidic medium is the critical point, which results in pyrrole **1** by a one-pot procedure and for which only a simple separation between **1** and benzophenone is needed at the end. We first used 2.5 N aqueous HCl (method A). Then, we realized that the nonnucleophilic oxalic acid might give better results (method B). However, the yield (58%) was lower than that obtained by in method A (65%). We then used glacial acetic acid (method C), which gave us a mixture of the new 1-acetyl-3-cyano-4-methylpyrrole and 3-cyano-4-methyl-1*H*-pyrrole (**1**) in a 2:3 ratio in 50% yield. This indicates that method A is the preferable one. On the basis of the aqueous HCl procedure, it is expected that scaling up the reaction will not be a problem.

We found that in the third step of the sequence, 3 equiv. of LDA led to an almost quantitative yield of (*E*/*Z*)-**6**. In the presence of only 2 equiv. of LDA, virtually no (*E*/*Z*)-**6** was formed. The (diphenylmethylene)amino group is an amino protecting group par excellence in the well-known O'Donnell method for the synthesis of optically active α-amino acids.[12] For the synthesis of 3-[(diphenylmethylene)-amino]propionitrile (**5**), we used amination of acrylonitrile with phthalimide as an initial step and protection of free amino group of 3-aminopropionitrile with benzophenone imine later. For ^{15}N incorporation we initially chose the

amination of acrylonitrile with benzophenone imine.[13] This literature procedure has a long reaction time and low yield, which induced us to find a better method to prepare **5** starting with phthalimide. The additional advantage of this method is that phthalimide is commercially available in the ^{15}N-enriched form.

As far as we know, Wittig coupling has not previously been used in the synthesis of pyrroles. We feel that this preparation has a broad scope. A host of protected 3-aminopropionitriles will be easily available by amination of substituted acrylonitriles for the synthesis of 2-substituted 3-cyano 4-methylpyrroles. Also, a number of 1,1-dimethoxy ketone derivatives will be easily available by Riley oxidation of aldehydes and ketones.[14] This allows Scheme 1 to be extended further to synthesize analogous of **1** with different substituents in the 4-position.

The 1-NH of the pyrroles can also be easily substituted by other groups by simple base-catalyzed electrophilic reactions, for example, pyrrole **1** can be simply converted into the new 1-benzyl-3-cyano-4-methylpyrrole (**8**) in high yield by treating it with benzyl bromide in diethyl ether in the presence of KO*t*Bu and 18-crown-6 ether as catalyst (Scheme 1). All the spectroscopic properties of **8** are in agreement with the proposed structure. Besides the reaction of the NH group, the nitrile functionality can be converted into many other functional groups. The nitrile functional group of pyrrole **1** reacts with a slight excess of DIBAL-H to give 4-methyl-1*H*-pyrrole-3-aldehyde (**7**) in 82% yield. Aldehyde **7** is a new compound (see Scheme 1). In the ^1H and ^{13}C NMR spectra, the characteristic CHO peak is observed at δ = 9.87 and 186 ppm, respectively. The Fermi doublet resonance at 2768 and 2820 cm^{-1}[15] and the carbonyl stretching at 1658 cm^{-1} in the IR spectrum show the presence of the aldehyde functional group in the 3-position.

Conclusions

Acrylonitrile was converted into a Wittig reagent in a few simple steps with high yield. Coupling of this product with commercially available 1,1-dimethoxyacetone gives an intermediate with reactive groups in the 1,5-positions. Deprotection and cyclization of these groups in one step gives the otherwise-difficult-to-access 3-cyano-4-methylpyrrole **1**. This scheme also allows easy, site-directed, stable-isotope incorporation at any position or a combination of positions. The scope of this new Wittig approach is very broad, because many different unsaturated nitriles and 1,1-dimethoxy ketones are expected to undergo this reaction. Furthermore, Scheme 1 can be extended to synthesize other five-membered heterocycles such as furans, thiophenes, selenophenes, and so on by synthesizing the corresponding nitrile derivatives. The scope of the reaction is even wider for the nitrile functionality, as it can be easily converted into an aldehyde that opens a plethora of new systems.

Experimental Section

General: Reactions were monitored by using thin-layer chromatography (TLC) on Merck F254 silica gel 60 aluminium sheets, 0.2 mm: spots were visualized by treating with an oxidizing spray (2 g of $KMnO_4$ and 4 g of $NaHCO_3$ in 100 mL of water). Column chromatography was performed on Merck silica gel 60. ^1H NMR spectra were recorded with a Bruker WM-300 or Bruker AM-600 spectrometer with tetramethylsilane (TMS: δ = 0.00 ppm) as an internal standard. ^1H noise-decoupled ^{13}C spectra were recorded with Bruker WM-300 at 75 MHz or a Bruker AM-600 at 150 MHz. ^{15}N NMR spectra were recorded with Bruker WM-300 with respect to external NH_4NO_3 (saturated in H_2O/lock:$CDCl_3$, conversion constant = 22.3 ppm). Perkin–Elmer Paragon 1000 FTIR was used for IR measurements (neat). Mass spectra were recorded with a Finnigan MAT 900 equipped with a direct insertion probe (DIP) or with a Finnigan MAT 700-TSQ equipped with a custom-made electron-spray interface (ESI) and electron ionization (EI) in JEOL JMS SX/SX 102A (four sector mass spectrometer), coupled to a JEOL MS-MP9021D/UPD system program. All experiments were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Saturated solutions of NaCl and NH_4Cl refer to saturated solutions of the salt in water. All chemicals were purchased from Aldrich Fluka or Acros Chimica. [^{15}N]-Phthalimide and potassium [^{15}N]-phthalimide were purchased from Aldrich/Isotech.

β-Phthalimidopropionitrile (4): Phthalimide (3.0 g, 20 mmol), potassium phthalimide (0.3 g), and acrylonitrile (10 mL) were heated at reflux for 3 h and excess acrylonitrile was evaporated in vacuo to obtain product **4** (4.05, 20 mmol) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.81 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2), 4.01 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2), 7.28–7.91 (m, 4 H, C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.10 (CH_2), 33.50 (CH_2), 116.7 (CN), 123.6 (2×CH), 131.6 (2×C), 134.6 (2×CH), 167.5 (C=O) ppm. IR: $\tilde{\nu}$ = 2254, 1772, 1714, 1699, 1668, 1652, 1467, 1398, 1378 cm^{-1}.

β-[^{15}N]-Phthalimidopropionitrile (4a): Similarly, [^{15}N]-phthalimide (3.0 g, 20 mmol), potassium [^{15}N]-phthalimide (0.3 g), and acrylonitrile (10 mL) were heated at reflux to obtain product **4a** (4.05, 20 mmol) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.82 (td, $^3J_{H,H}$ = 6.9 Hz, $^2J_{H,^{15}N}$ = 2.2 Hz, 2 H, CH_2), 4.02 (td, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,^{15}N}$ = 1.1 Hz, 2 H, CH_2), 7.28–7.91 (m, 4 H, C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.13 (CH_2), 33.50 (d, $^1J_{C,^{15}N}$ = 10.5 Hz, CH_2), 116.8 (CN), 123.6 (2×CH), 131.6 (d, $^2J_{C,^{15}N}$ = 8.1 Hz, 2×C), 134.6 (2×CH), 167.5 (d, $^1J_{C,^{15}N}$ = 12.5 Hz, C=O) ppm. ^{15}N NMR (30 MHz, $CDCl_3$): δ = 158.5 ppm. IR: $\tilde{\nu}$ = 2253, 1772, 1713, 1610, 1394, 1367 cm^{-1}. MS (EI+): *m*/*z* = 201, 162, 133, 104, 76. HRMS: calcd. for $C_{11}H_8N^{15}NO_2$ 201.058578; found 201.0559.

3-[(Diphenylmethylene)amino]propionitrile (5): β-Phthalimidopropionitrile (**4**; 4.05 g, 20 mmol) in ethanol (100 mL) was heated at reflux with hydrazine hydrate (50–60%, 7 mL) for 15 min. The solid was filtered off. The solvent was concentrated and extracted with diethyl ether (3×200 mL) after adding 10% NaOH (to pH 10). The solvent was concentrated to 50 mL and an ethanol solution of fumaric acid (1.16 g, 10 mmol) was added. The mixture was stirred for 16 h and filtered to obtain the solid product of 3-aminopropionitrile fumarate (2.30 g, 18 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2), 2.88 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, CH_2), 6.42 (s, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.82 (CH_2), 36.64 (CH_2), 119.2 (CN), 135.1 (2×CH), 168.0 (C=O) ppm. IR: $\tilde{\nu}$ = 2736 (br.), 2256, 1644, 1520, 1506, 1471, 1358, 1219 cm^{-1}.

To a solution of 3-aminopropionitrile fumarate (2.30 g, 18 mmol) in acetic acid (20 mL) was added benzophenone imine (3.27 g, 18 mmol) at room temperature. The reaction mixture was stirred

for 16 h at room temperature. Ethyl acetate/*n*-hexane (1:3, 100 mL) was added to the solution and stirred further for 1 h at room temperature. The mixture was filtered and washed with ethyl acetate/*n*-hexane (1:3). The filtrate was concentrated to 50 mL and *n*-hexane (20 mL) was added to obtain a colorless crystalline solid. The product was filtered, dissolved in CH_2Cl_2 (20 mL), and washed with 10% $NaHCO_3$, dried with $MgSO_4$, and filtered, and the solvent was evaporated to obtain product **5** (3.51 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, CH_2), 3.60 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, CH_2), 7.16–7.64 (m, 10 H, 2 × C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.77 (CH_2), 48.91 (CH_2), 118.7 (CN), 127.5, 128.0, 128.5, 128.7, 128.8, 130.4, 135.9, 138.9 (2 × C_6H_5), 170.8 (C=N) ppm. IR: $\tilde{\nu}$ = 2247, 1622, 1595, 1575, 1490, 1445, 1408, 1315, 1286 cm^{-1}.

[3-^{15}N]-[(Diphenylmethylene)amino]propionitrile (5a): Similarly, β-[^{15}N]-phthalimidopropionitrile (**4a**) was treated with hydrazine hydrate. The ethanol solution of 3-aminopropionitrile and fumaric acid yielded [3-^{15}N]-aminopropionitrile fumarate (2.30 g, 18 mmol).^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64 (td, $^3J_{H,H}$ = 6.8 Hz, $^2J_{H,^{15}N}$ = 1.9 Hz, 2 H, CH_2), 2.88 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2), 6.42 (s, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.47 (CH_2), 36.42 (d, $^1J_{C,^{15}N}$ = 5.1 Hz, CH_2), 119.2 (CN), 135.1 (2 × CH), 168.0 (C=O) ppm. ^{15}N NMR (30 MHz, $CDCl_3$): δ = 29.30 ppm. IR: $\tilde{\nu}$ = 2736 (br.), 2258, 1645, 1520, 1506, 1472, 1358, 1232 cm^{-1}.

Similarly, [3-^{15}N]-[(diphenylmethylene)amino]propionitrile **5a** (3.51 g, 83%) was obtained from [3-^{15}N]-aminopropionitrile fumarate (2.30 g, 18 mmol) and benzophenone imine (3.27 g, 18 mmol) as a light-yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.72 (td, $^3J_{H,H}$ = 6.7 Hz, $^2J_{H,^{15}N}$ = 2.8 Hz, 2 H, CH_2), 3.58 (td, $^3J_{H,H}$ = 6.7 Hz, $^3J_{H,^{15}N}$ = 1.0 Hz, 2 H, CH_2), 7.16–7.64 (m, 10 H, 2 × C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.83 (d, $^1J_{C,^{15}N}$ = 5.1 Hz, CH_2), 48.92 (CH_2), 118.7 (CN), 127.5–139.0 (2 × C_6H_5), 170.6 (d, $^1J_{C,^{15}N}$ = 5.6 Hz, C=N) ppm. ^{15}N NMR (30 MHz, $CDCl_3$): δ = 315.4 ppm. IR: $\tilde{\nu}$ = 2246, 1660, 1608, 1592, 1568, 1489, 1445, 14408, 1316, 1276 cm^{-1}. MS (EI+): *m*/*z* = 235, 195, 105, 91. HRMS: calcd. for $^{12}C_{16}{}^1H_{14}{}^{14}N^{15}N$ 235.11569; found 235.1134.

Mixture of (2*E*)- and (2*Z*)-2-{[(Diphenylmethylene)amino]methyl}-4,4-dimethoxy-3-methylbut-2-enenitrile (6): A solution of LDA (45 mmol) was prepared by the addition of *n*BuLi (1.6 M in hexanes, 28 mL, 45 mmol) to a solution of diisopropylamine (4.60 g, 45 mmol) in THF (150 mL) at –70 °C. Compound **5** (3.51 g, 15 mmol) in THF (25 mL) was added dropwise to this solution. The reaction mixture was stirred 15 min at –70 °C, followed by the addition of a solution of diethyl chlorophosphate (2.58 g, 15 mmol) in THF (25 mL). After 30 min, a solution of 1,1-dimethoxyacetone (1.90 g, 16 mmol) in THF (25 mL) was added dropwise. The reaction mixture was warmed to room temperature over approximately 2 h and further stirred 2 h at room temperature. Work up was accomplished by adding saturated NH_4Cl (100 mL) and saturated NaCl (100 mL). The mixture was extracted with diethyl ether (3 × 200 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil. The product was purified by column chromatography (silica gel 60; ethyl acetate/*n*-hexane, 1:3) to afford **6** (4.35 g, 87%) as a mixture of (*E*/*Z*) isomers in a 3:2 ratio as a light-yellow oil. R_f = 0.40 (ethyl acetate/*n*-hexane, 1:3). ^{1}H NMR [300 MHz, $CDCl_3$, (*E*) isomer]: δ = 2.08 (s, 3 H, CH_3), 3.26 (s, 6 H, OCH_3), 4.21 (s, 2 H, CH_2), 4.91 (s, 1 H, CH), 7.19–7.66 [m, 20 H, C_6H_5, (*E*/*Z*) isomers] ppm. ^{13}C NMR [75 MHz, $CDCl_3$, (*E*) isomer]: δ = 17.33 (CH_3), 51.14 (CH_2), 54.15 (OCH_3), 100.9 (CH), 113.5 (=*C*-CN), 117.8 (CN), 125.4, 125.7, 127.4, 127.6, 127.7, 128.0, 128.6, 128.7, 128.8, 130.4, 135.9, 139.0 [C_6H_5, (*E*/*Z*) isomers], 152.1 (CH_3-*C*=), 170.4 (-*C*=N) ppm. ^{1}H NMR [300 MHz, $CDCl_3$ (*Z*) isomer]: δ = 1.74 (s, 3 H, CH_3), 3.43 (s, 6 H, OCH_3), 4.16 (s, 2 H, CH_2), 5.15 (s, 1 H, CH) ppm. NOE observed between 1.74 (CH_3) and 4.16 (CH_2) ppm in (*Z*) isomer. ^{13}C NMR [75 MHz, $CDCl_3$, (Z) isomer]: δ = 12.17 (CH_3), 51.75 (CH_2), 55.38 (OCH_3), 105.3 (CH), 112.5 (=*C*-CN), 117.0 (CN), 151.8 (CH_3-*C*=), 170.8 (-*C*=N) ppm. IR: $\tilde{\nu}$ = 2934, 2215, 1736, 1623, 1576, 1445, 1209, 1102, 1066 cm^{-1}.

Mixture of (2*E*)- and (2*Z*)-[^{15}N]-2-{[(Diphenylmethylene)amino]methyl}-4,4-dimethoxy-3-methylbut-2-enenitrile (6a): Similarly, [^{15}N]-**5a** (3.51 g, 15 mmol) yielded **6a** (4.35 g, 87%) as a mixture of (*E*/*Z*) isomers in a 3:2 ratio as a light-yellow oil. ^{1}H NMR [300 MHz, $CDCl_3$, (*Z*/*E*) isomers]: δ = 4.16 (m, CH_2), 4.20 (m, CH_2) ppm. ^{13}C NMR [75 MHz, $CDCl_3$, (*Z*/*E*) isomers]: δ = 51.75 (d, $^1J_{C,^{15}N}$ = 1.6 Hz, CH_2), 51.14 (d, $^1J_{C,^{15}N}$ = 1.6 Hz, CH_2) ppm. ^{15}N NMR [30 MHz, $CDCl_3$, (*Z*/*E*) isomers]: δ = 313.1, 314.7 ppm.

3-Cyano-4-methyl-1*H*-pyrrole (1)

Method A: HCl (2.5 N, 50 mL) was added to (*E*/*Z*)-**6** (4.35 g, 13 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was extracted with CH_2Cl_2 (2 × 100 mL), washed with 10% $NaHCO_3$, dried with $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure. The product was separated from benzophenone by column chromatography (silica gel 60; ethyl acetate/*n*-hexane, 1:3) to yield **1** (0.89 g, 65%) as a light-yellow solid. R_f = 0.22 (ethyl acetate/*n*-hexane, 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.19 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, CH_3), 6.57 (m, 1 H, 5-CH), 7.27 (dd, $^3J_{H,H}$ = 3.0 Hz, $^4J_{H,H}$ = 2.4 Hz, 1 H, 2-CH), 8.92 (br., 1 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.29 (CH_3), 93.82 (3-C), 116.7 (5-CH), 116.8 (CN), 122.0 (4-C), 125.3 (2-CH) ppm. IR: $\tilde{\nu}$ = 3270, 2230, 1560, 1524, 1449, 1239, 1175, 1102, 1069 cm^{-1}. MS (EI): *m*/*z* (%) = 105 (100), 106 (82), 107 (11), 78 (20).

Method B: To a solution of (*E*/*Z*)-**6** (4.35 g, 13 mmol) in ethyl acetate (50 mL) was added 10% aqueous solution of oxalic acid (50 mL), and the mixture was heated at reflux for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL), washed with 10% $NaHCO_3$ (100 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield a light-yellow oil. Product **1** (R_f = 0.22) was separated from benzophenone (R_f = 0.45) by column chromatography (silica gel 60; ethyl acetate/*n*-hexane, 1:3) to yield light-yellow solid **1** (0.8 g, 58%).

Method C: A solution of (*E*/*Z*)-**6** (4.35 g, 13 mmol) in glacial acetic acid (50 mL) was heated at reflux for 1 h. The solvent was removed under reduced pressure to yield a light-yellow oil. The products were separated from benzophenone by column chromatography (silica gel 60; ethyl acetate/hexane, 1:3) to yield light-yellow solid mixtures of **1** and 1-acetyl-3-cyano-4-methylpyrrole in a 6:4 ratio (0.85 g). 1-Acetyl-3-cyano-4-methylpyrrole (0.34 g) (R_f = 0.42; ethyl acetate/hexane, 1:1, 1% Et_3N) was further separated from pyrrole **1** (0.4 g) by column chromatography (silica gel 60; ethyl acetate/hexane, 1:1, 1% Et_3N) as a light-yellow solid. Data for 1-acetyl-3-cyano-4-methylpyrrole: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.18 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 7.09 (s, 1 H, 5-CH), 7.70 (s, 1 H, 2-CH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.44 (CH_3), 22.02 (*C*H_3-C=O), 100.2 (3-C), 114.5 (CN), 117.4 (5-CH), 125.9 (4-C), 128.9 (2-CH), 166.6 (C=O) ppm. IR: $\tilde{\nu}$ = 3132, 2228, 1728, 1652, 1519, 1385, 1354, 1318, 1227, 1215, 1075 cm^{-1}.

1-Acetyl-3-cyano-4-methylpyrrole (0.34 g, 2.3 mmol) was treated with 10% NaOH (10 mL) and stirred for 12 h at room temperature, neutralized with 2 N HCl, and extracted with diethyl ether (3 × 50 mL). The solvent was washed with saturated NaCl, dried

with $MgSO_4$, and filtered. The solvent was evaporated to get yellow solid of pyrrole **1** (0.21 g, 87%).

[1-^{15}N]-3-Cyano-4-methyl-1*H*-pyrrole (1a): Similarly, (*E*/*Z*)-**6** (4.35 g, 13 mmol) in 2.5 N HCl (20 mL, method A) yielded **1a** (0.81 g, 59%) as a light-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, CH_3), 6.57 (m, 1 H, 5-CH), 7.21 (m, 1 H, 2-CH), 9.11 (ddd, $^1J_{H,^{15}N}$ = 97.9 Hz, $^3J_{H,H}$ = 2.5 Hz, $^3J_{H,H}$ = 2.5 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.27 (CH_3), 93.77 (d, $^2J_{C,^{15}N}$ = 5.5 Hz, 3-C), 116.7 (d, $^1J_{C,^{15}N}$ = 12.8 Hz, 5-CH), 116.8 (CN), 122.0 (d, $^2J_{C,^{15}N}$ = 2.9 Hz, 4-C), 125.3 (d, $^1J_{C,^{15}N}$ = 14.5 Hz, 2-CH) ppm. ^{15}N NMR (30 MHz, $CDCl_3$): δ = 153.0 ppm.[9] IR: $\tilde{\nu}$ = 3290, 2219, 1560, 1516, 1443, 1309, 1237 cm^{-1}. MS (EI+): *m*/*z* (%) = 106 (100), 107 (78), 108 (37), 78 (6). HRMS: calcd. for $C_6H_6N^{15}N$ 107.05309; found 107.0505.

4-Methyl-1*H*-pyrrole-3-aldehyde (7): To a solution of **1** (0.76 g, 7.2 mmol) in diethyl ether (100 mL) cooled to –60 °C was added DIBAL-H (1 N in *n*-hexane, 10 mL, 10 mmol). The reaction mixture was warmed up to –30 °C over 1 h and then stirred for 1 h at room temperature. A homogeneous mixture of silica gel/water (8 g/3 mL) was added to the mixture and continued to stir 1 h at 0 °C and further 1 h at room temperature. Then, K_2CO_3 (12 g) and $MgSO_4$ (12 g) were added to the solution, and the mixture was stirred for 1 h at room temperature. The mixture was filtered and washed thoroughly with diethyl ether. The solvent was removed under reduced pressure to yield yellow solid of **7** (0.64 g, 82%). R_f = 0.47 (diethyl ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.33 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, CH_3), 6.58 (m, 1 H, 5-CH), 7.34 (dd, $^3J_{H,H}$ = 3.3 Hz, $^4J_{H,H}$ = 2.4 Hz, 1 H, 2-CH), 8.57 (br., 1 H, NH), 9.87 (s, 1 H, CHO) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.0 (CH_3), 118.3 (5-CH), 120.2 (3-C), 125.1 (4-C), 127.9 (2-CH), 186.2 (C=O) ppm. IR: $\tilde{\nu}$ = 3264, 2920, 2826, 2768, 1658, 1651, 1654, 1515 cm^{-1}. MS (EI): *m*/*z* (%) = 109 (92), 108 (100), 80 (24), 53 (21).

1-Benzyl-3-cyano-4-methylpyrrole (8): KO*t*Bu (0.34 g, 3 mmol) was added to a solution of 18-crown-6 (0.13 g, 0.5 mmol) in diethyl ether (20 mL) at room temperature. To the mixture was added **1** (0.24 g, 2.3 mmol) in diethyl ether (10 mL) and after 15 min stirring followed by the addition of benzyl bromide (0.52 g, 3 mmol). The reaction was stirred under a N_2 atmosphere for 18 h at room temperature. The reaction was quenched by the addition of water (20 mL). Ether phase was separated and aqueous phase was extracted with diethyl ether (3 × 50 mL). The ether phase was washed with saturated NaCl and dried with $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. Purification by column chromatography (silica gel 60; ethyl acetate/*n*-hexane, 1:3) afforded yellow solid of product **8** (0.38 g, 85%). R_f = 0.42 (ethyl acetate/*n*-hexane, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 4.98 (s, 2 H CH_2), 6.41 (m, 1 H, 5-CH), 7.05 (d, $^4J_{H,H}$ = 1.84 Hz, 1 H, 2-CH), 7.25–7.38 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.51 (CH_3), 53.85 (CH_2), 94.03 (3-C), 116.3 (CN), 119.9 (5-CH), 123.2 (4-C), 127.2 (3′-CH, 5′-CH, C_6H_5), 127.5 (2-CH), 128.3 (4′-CH, C_6H_5), 128.9 (2′-CH, 6′-CH, C_6H_5), 136.0 (1′-C) ppm. IR: $\tilde{\nu}$ = 3124, 2209, 1525, 1495, 1358, 1149 cm^{-1}. MS (ESI): *m*/*z* = 197 $[M + H]^+$.

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