Synthesis of 1-Vinylpyrrole-imidazole Alkaloids

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Abstract: The reaction between 1-methylimidazole, cyano(phenyl)acetylene, and 1-vinylpyrrole-2-carbaldehydes (MeCN, 20–25 °C) stereoselectively gives 1-vinylpyrrole-imidazole ensembles with a (*Z*,*Z*)-bis(2-cyano-1-phenylvinyl)oxy function in up to 45% yield. Unlike recently reported three-component reaction between imidazoles, electron-deficient acetylenes, and aldehydes affording 1:1:1 adducts, in this case two molecules of acetylene are involved to deliver 1:2:1 adducts thus representing a novel functionalizaton of the pyrrole-imidazole alkaloid scaffold. The initial zwitterion generated from imidazole and cyano(phenyl)acetylene is thought to be transformed into a carbene, which reacts with pyrrole-2-carbaldehyde. Two subsequent rearrangements of the 1:1:1 adduct furnish the intermediate pyrrole-imidazole ensemble, which in its enol form adds to second molecule of cyano(phenyl)acetylene to yield the final products, functionalized pyrrole-imidazole alkaloids.

Key words: 1-methylimidazole, cyano(phenyl)acetylene, 1-vinylpyrrole-2-carbaldehydes, three-component reaction, pyrrole-imidazole alkaloids

Over the last decade, the functionalized polycyclic pyrrole-imidazole alkaloids (PIAs) have attracted growing interest due to their challenging molecular structure and biological activity.[1,2] The PIA family comprises of hundreds of secondary metabolites from marine sponges. In the parent representative of PIAs, oroidin, the pyrrole and imidazole rings, bearing amido and amino functions and two bromine atoms, are bridged by a propenyl chain. These pyrrole-imidazole ensembles are potent antifungal agents[2a,c] and exhibit antihistaminic activity.[2b] A congener of this series, ageladine A, is an unique inhibitor of matrix metalloproteinases at micromolar concentrations.[2d]

Pyrrole-imidazole polyamides bind the minor groove of DNA sequence-specifically, encoded by side-by-side arrangements of 1-methylpyrrole- and 1-methylimidazole-carboxamide monomers.[2e] The outstanding biological properties of PIAs include fish feeding deterrency and antibiofilm activity.[2f]

This is why so much attention is now paid to the synthesis of oroidin-related alkaloids. These efforts include the synthesis of midpacamide which differs from oroidin by the 1-methyl substituent in the pyrrole rings, functionalized three-carbon bridge, and two carbonyl groups in the imidazole ring. Another recently synthesized representative of PIAs family is dispacamide having an isomerized alkenyl chain and imidazolinone ring.[3a]

Condensation of 5-amino-3-(pyrrol-2-yl)pyrazoles with imidazolecarbaldehydes led to polycyclic pyrrole-imidazole-pyrazole ensembles.[3b] Enantioselective addition of pyrroles to α,β-unsaturated 2-acylimidazoles gave another series of PIAs.[3c] Dipyrromethanes with imidazole substituents in the *meso*-position were employed in the synthesis of imidazole-substituted porphyrins.[3d] 1-Vinylpyrrole-benzimidazole ensembles were synthesized by the condensation of 1-vinyl-1*H*-pyrrole-2-carbaldehydes with *o*-phenylenediamine.[3e]

These endeavors towards the search for new methodologies for the synthesis of PIAs keep being extended. The present paper is a conceptually new contribution to this area. Recently, we have pioneered a new methodology for imidazole ring functionalization via zwitterionic intermediates generated by nucleophilic addition of 1-substituted imidazoles to electron-deficient acetylenes.[4] The methodology constitutes a three-component reaction between 1-substituted imidazoles, electron-deficient acetylenes, and aldehydes to deliver the 1:1:1 adducts, imidazoles functionalized at the C2-position by enol-[5a] or carbonyl-containing moieties.[5b]

In an attempt to extend the above methodology to pyrrolecarbaldehydes, we have unexpectedly revealed that this three-component reaction, unlike the previously reported version,[5] takes another direction: instead of 1:1:1 adducts, the 1:2:1 adducts are assembled, thus indicating that a second molecule of acetylene is involved. Therefore, here we report the three-component reaction between 1-methyl-1*H*-imidazole (**1**), cyano(phenyl)acetylene (**2**), and 1-vinyl-1*H*-pyrrole-2-carbaldehydes **3a–e**. The choice of 1-vinylpyrrolecarbaldehydes **3** was due to the high synthetic potential of the expected products secured by the reactive 1-vinyl group in their molecules and also to their availability by recent successful formylation of 1-vinylpyrroles.[6]

According to the previous publications on the three-component reactions between 1-substituted imidazoles, electron-deficient acetylenes, and aldehydes, in this case the reaction might result in the formation of the C2-functionalized imidazoles either of enol **A** or cyanoacetophenone **B** types or both; these are 1:1:1 adducts.

In fact, when the reactants **1**, **2**, and **3** were mixed at room temperature (20–25 °C) in acetonitrile, neither adducts of

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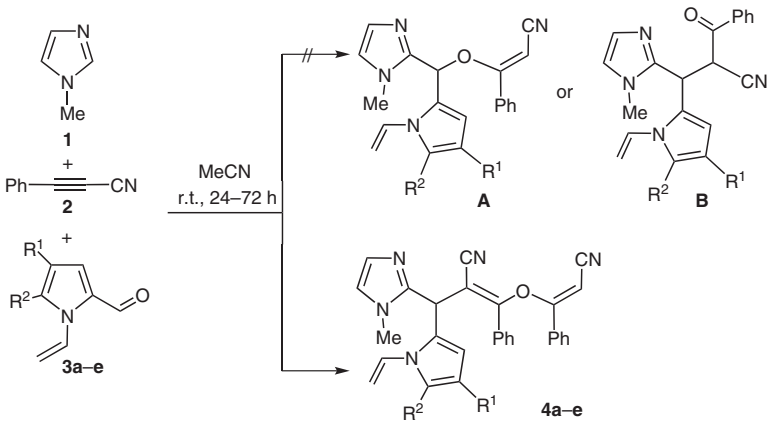
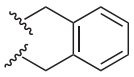
Table 1 Synthesis of Pyrrole-imidazole Ensembles **4a–e** from 1-Methyl-1*H*-imidazole (**1**), Cyano(phenyl)acetylene (**2**), and 1-Vinylpyrrole-2-carbaldehydes **3a–e**[a]



Entry	Pyrrole **3**	R^1	R^2	Product	Isolated yield (%)	Conversion (%)
1	**3a**	H	H	**4a**	42	75
2	**3b**	H	Ph	**4b**	33	66
3	**3c**	H	4-$MeOC_6H_4$	**4c**	45	49
4	**3d**	$-(CH_2)_4-$		**4d**	14	42
5	**3e**			**4e**	43	41

[a] Molar ratio **1/2/3** = 1:2:1.

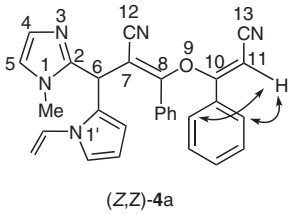
type **A** nor those of type **B** were detected among the reaction products. Instead, 1:2:1 adducts **4a–e**, [(1-vinylpyrrol-2-yl)-1-methylimidazol-2-yl]methanes containing the (*Z*,*Z*)-bis(2-cyano-1-phenylvinyl)oxy moiety in the methine bridge, i.e. the ensembles incorporating a second molecule of acetylene, were isolated (Table 1).

As expected, the yields of **4a–e** proved to be dependent of the ratio of the reactants: at the molar ratio **1/2/3** 1:2:1, the yields of ensembles **4a–e** were in the range 14–45%. At the equimolar reactants ratio, the yields of ensembles **4a–e** dropped to 7–12%, but the 1:1:1 adducts **A** and **B** remained undetectable. The reaction is strictly stereospecific: both vinyl moieties are formed in *Z*-configuration only. The reaction progress was controlled by acetylene **2** consumption and was stopped when the IR spectra of the reaction mixture the broad intense absorption band of the C≡C–CN bond (2260–2280 cm^{-1}) was completely replaced by the narrow absorption band of the C=C–CN bond (2216–2219 cm^{-1}) belonging to the end products **4a–e**. For most aldehydes **3a–e**, the reaction time was 24–26 hours, and only in the case of dihydrobenzo[*g*]indole-derived aldehyde **3e** it took 72 hours, obviously due to steric hindrance. In all the cases, by the moment of full consumption of acetylene **2**, 25–59% of the starting aldehydes **3a–e** were recovered (Table 1). Such an incomplete conversion of aldehydes **3a–e** is in accordance with the involvement of two molecules of acetylene **2** in the reaction and also with the expected anionic oligomerization of this acetylene initiated by carbanionic center of initial zwitterion as reported previously.[4c] Apparently, the modest yields of ensembles **4a–e** can be accounted for the same oligomerization.

The ensembles **4a–e** are colored (orange, brown) oils soluble in conventional organic solvents. Their structures have been proved by NMR (^1H, ^{13}C, ^{15}N) spectroscopy using 2D techniques (COSY, NOESY, HMBC, HSQC) and mass spectrometry.

In ^1H NMR spectra of ensembles **4a–e**, singlets of the vinyl protons (H11) are observed at δ = 5.04–5.12 ppm. The divinyl moiety of ensembles **4a–e** is manifested in the ^{13}C NMR spectrum by the signals in the region δ = 100.8–101.7 (C7), 162.2–162.5 (C8), 168.2–168.6 (C10), and 83.5–83.7 (C11) ppm. The nitrile C-atoms resonate at δ = 116.8–117.1 (12-CN) and 115.0–115.1 (13-CN).

According to the NOESY spectra, the products **4a–e** are (*Z*)-isomers: the cross-peaks between olefinic proton H11 and *ortho*-protons of phenyl are observed (Figure 1).



(*Z*,Z)-**4**a

Figure 1 Cross-peaks in the 2D NOESY spectrum of ensemble **4a**

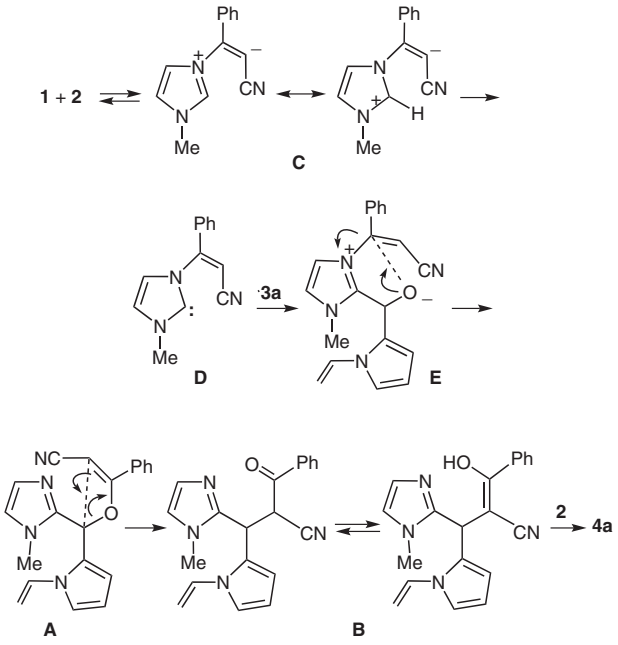
In ^{1}H, ^{13}C, and ^{15}N NMR spectra of ensembles **4**, the following signals of the imidazole ring are present: H4, H5 (for **4a**); C2, C4, C5 and N1, N1′, N3. The C2 atom lacks a proton which confirms the location of the substituent at the 2-position of the imidazole ring. In the ^{13}C NMR spectra of compounds **4**, the signals of C4 and C5 have the similar values as in starting imidazole, while the C2 signal is shifted downfield (from δ = 136 to 145 ppm) by the negative inductive effect of the substituent and becomes quaternary. As expected, in the ^{15}N NMR spectrum of the compound **4a**, the N1 and N3 nuclei resonate at different regions δ = –223 and –119 ppm, respectively, and N1′ at –208.9 ppm.

IR spectra of ensembles **4** are in agreement with their structure: the bands at 2216–2219 cm^{-1} belonging to the CN group at the double bond and the C=C absorption band at 1640–1650 cm^{-1} are observed; the strong absorption band in the region 1023–1131 cm^{-1} is attributed to the C–O–C bonds.

The formation of ensembles **4a–e** can be tentatively represented as depicted in Scheme 1 (on the example of pyrrole-2-carbaldehyde **3a**). Presumably, as in the case of similar reactions with aliphatic[5a] and aromatic[5b] aldehydes, the reaction is triggered by the nucleophilic attack of imidazole **1** at the triple bond of acetylene **2** to generate the intermediate zwitterion **C** of *Z*-configuration (in keeping with the rule of *trans*-nucleophilic addition to acetylenes[7]), which uptakes the proton (by its carbanion center) from the imidazole 2-position to form carbene **D**. Apparently, this proton transfer occurs rather in an intermolecular than in intramolecular fashion, i.e. with the participation of second zwitterionic molecule, that is supported by recent quantum chemical calculations for zwitterions **C**.[8] Further on, the carbene **D** inserts into the C=O bond of aldehyde **3a** to form oxygen-centered zwitterion **E** and the subsequent migration of the vinyl moiety from $N3^{+}$ atom to oxygen anionic center leads to intermediate vinyl ether **A**. Next step is assumed to be the rearrangement of the intermediate **A** to cyanoacetophenone **B** which is added in its enol form to the second molecule of acetylene **2** thus completing the assembly of the final product **4a**.

As already mentioned, unlike the cases with aliphatic and aromatic aldehydes, this reaction includes the additional step involving the second molecule of acetylene to deliver the (*Z*,*Z*)-bis(2-cyano-1-phenylvinyl)oxy moiety.

In summary, the three-component reaction between 1-methylimidazole, cyano(phenyl)acetylene, and 1-vinylpyrrole-2-carbaldehydes, unlike the similar reactions with aliphatic or aromatic aldehydes, proceeds with involvement of two molecules of cyano(phenyl)acetylene to afford 1:2:1 adducts, [(1-vinylpyrrol-2-yl)-1-methylimidazol-2-yl]methanes with (*Z*,*Z*)-bis(2-cyano-1-phenylvinyl)oxy substituent in the methine bridge, which represent a basically new family of PIAs. The cyano groups in their molecules are potentially convertible into the amido and amino functions, which commonly occur in PIAs isolated from marine sponges. Thus, the elaborated conceptually new methodology represents a short-cut to a new family of densely functionalized PIAs bearing reactive N-vinyl group in the pyrrole moiety.



Scheme 1 Tentative reaction sequence for the three-component interaction between 1-methyl-1*H*-imidazole (**1**), cyano(phenyl)acetylene (**2**), and 1-vinyl-1*H*-pyrrole-2-carbaldehyde (**3a**)

IR spectra were measured on a IFS 25 instruments. ^{1}H, ^{13}C, and ^{15}N NMR and 2D NOESY spectra were recorded with a Bruker BioSpin AV-400 spectrometer with HMDS as an internal standard. Labeling of carbon and hydrogen atoms in the compounds **4a–e** (on the example of **4a**) are given in Figure 2. Mass spectra were recorded on a GCMS-QP5050A spectrometer made by Shimadzu Company (mass analyzer: quadrupole, electron ionization, mass range 40-700 Da). Injection the samples was carried out using a system of direct input DI-50, temperature recording was 160 °C, ion source temperature 200 °C. Column chromatography and TLC were carried out on neutral alumina with $CHCl_3$–benzene–EtOH, 20:4:1. 1-Methyl-1*H*-imidazole (**1**) is commercially available, cyano(phenyl)acetylene (**2**) was prepared according to a known procedure,[9] and 1-vinylpyrrole-2-carbaldehydes **3a–e** were obtained by a literature procedure.[6]

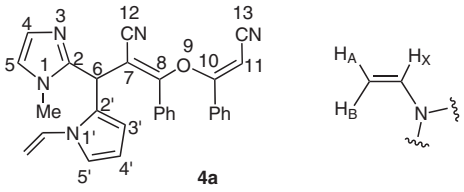


Figure 2 Labeling of hydrogen and carbon atoms in compound **4a** used for NMR peak assignments

(*Z*)-3-{[(*Z*)-2-Cyano-1-phenylvinyl]oxy}-2-[(1-methyl-1*H*-imidazol-2-yl)(1-vinyl-1*H*-pyrrol-2-yl)methyl]-3-phenylprop-2-enenitrile (4a); Typical Procedure

To a mixture of acetylene **2** (0.254 g, 2 mmol) and pyrrole-2-carbaldehyde **3a** (0.121 g, 1 mmol) in MeCN (0.5 mL) was added 1-methyl-1*H*-imidazole (**1**, 0.082 g, 1 mmol) in MeCN (0.5 mL). The mixture

was stirred at 20–25 °C for 24 h. Column chromatography afforded compound **4a** as an orange oil; yield: 0.146 g (42%). Initial pyrrole-2-carbaldehyde **3a** was recovered (0.030 g, conversion was 75%).

IR (microlayer): 1027, 1076, 1113, 1126 (C–O–C), 1643 (C=C), 2219 cm^{-1} (CN).

^1H NMR (400.13 MHz, $CDCl_3$): δ = 3.47 (s, 3 H, NCH_3), 4.91 (d, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_A), 5.12 (s, 1 H, H11), 5.20 (d, $^3J_{HB,HX}$ = 15.7 Hz, 1 H, H_B), 5.89 (s, 1 H, H6), 6.00 (2 d, $^3J_{H3',H4'}$ = 3.7 Hz, $^4J_{H3',H5'}$ = 1.7 Hz, 1 H, H3′), 6.16 (2 d, $^3J_{H4',H5'}$ = 3.1 Hz, 1 H, H4′), 6.90 (s, 1 H, H5), 7.04 (2 d, 1 H, H5′), 7.09 (2 d, $^3J_{HB,HX}$ = 15.7 Hz, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_X), 7.11 (s, 1 H, H4), 7.10–7.30 (m, 10 H, 2 Ph).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 33.1 (NCH_3), 34.6 (C6), 83.7 (C11), 100.8 (C7), 101.1 (N1′-CH_AH_B), 109.9 (C4′), 111.1 (C3′), 115.0 (13-CN), 116.8 (12-CN), 118.7 (C5′), 122.1 (C5), 126.3 (C8-*o*-C_{Ph}), 126.8 (C2′), 127.8 (C4), 128.2 (C8-*p*-C_{Ph}, C10-*o*-C_{Ph}), 128.7 (C10-*m*-C_{Ph}), 128.8 (C8-*m*-C_{Ph}), 130.0 (N1′-CH_X), 130.8 (C10-*p*-C_{Ph}), 131.4 (C10-*i*-C_{Ph}), 131.7 (C8-*i*-C_{Ph}), 143.9 (C2), 162.5 (C8), 168.2 (C10).

^{15}N NMR (40.55 MHz, $CDCl_3$): δ = –222.9 (N1), –208.9 (N1′), –118.7 (N3), –112.9 (13-CN).

Anal. Calcd for $C_{29}H_{23}N_5O$: C, 76.13; H, 5.07; N, 15.31. Found: C, 76.27; H, 5.03; N, 15.45.

(*Z*)-3-{[(*Z*)-2-Cyano-1-phenylvinyl]oxy}-2-[(1-methyl-1*H*-imidazol-2-yl)(5-phenyl-1-vinyl-1*H*-pyrrol-2-yl)methyl]-3-phenylprop-2-enenitrile (4b)

Following the typical procedure for **4a** using acetylene **2** (0.254 g, 2 mmol), pyrrole-2-carbaldehyde **3b** (0.197 g, 1 mmol), and 1-methyl-1*H*-imidazole (**1**, 0.082 g, 1 mmol) in MeCN (0.5 mL) at 20–25 °C for 24 h gave **4b** as a dark orange oil; yield: 0.119 g (33%). Initial pyrrole-2-carbaldehyde **3b** was recovered (0.067 g, conversion was 66%).

IR (microlayer): 1028, 1042, 1076, 1114 (C–O–C), 1643 (C=C), 2219 cm^{-1} (CN).

^1H NMR (400.13 MHz, $CDCl_3$): δ = 3.50 (s, 3 H, NCH_3), 5.06 (s, 1 H, H11), 5.14 (d, $^3J_{HB,HX}$ = 15.7 Hz, 1 H, H_B), 5.39 (d, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_A), 5.99 (s, 1 H, H6), 6.18 (d, 1 H, H3′), 6.28 (d, $^3J_{H4',H3'}$ = 3.9 Hz, 1 H, H4′), 6.89 (s, 1 H, H5), 7.08 (2 d, $^3J_{HB,HX}$ = 15.7 Hz, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_X), 7.11 (s, 1 H, H4), 7.10–7.50 (m, 15 H, 3 Ph).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 33.1 (NCH_3), 34.9 (C6), 83.6 (C11), 101.4 (C7), 110.2 (N1′-CH_AH_B), 111.4 (C3′), 112.8 (C4′), 115.1 (13-CN), 117.0 (12-CN), 121.8 (C5), 126.5 (C8-*o*-C_{Ph}), 126.8 (C2′), 127.8 (C4), 128.2 (C8-*p*-C_{Ph}), 128.3 (C10-*o*-C_{Ph}, C5′-*o*-C_{Ph}), 128.7 (C5′-*m*-C_{Ph}), 128.9 (C8-*m*-C_{Ph}, C10-*m*-C_{Ph}), 130.7 (C5′), 130.8 (N1′-CH_X), 131.3 (C10-*i*-C_{Ph}), 131.6 (C8-*i*-C_{Ph}), 131.7 (C10-*p*-C_{Ph}), 133.0 (C5′-*p*-C_{Ph}), 135.2 (C5′-*i*-C_{Ph}), 144.8 (C2), 162.4 (C8), 168.5 (C10).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{28}N_5O$: 533.22; found: 533.10.

Anal. Calcd for $C_{35}H_{27}N_5O$: C, 78.78; H, 5.10; N, 13.12. Found: C, 78.24; H, 4.98; N, 13.09.

(*Z*)-3-{[(*Z*)-2-Cyano-1-phenylvinyl]oxy}-2-[5-(4-methoxyphenyl)-1-vinyl-1*H*-pyrrol-2-yl](1-methyl-1*H*-imidazol-2-yl)methyl]-3-phenyl-2-propenenitrile (4c)

Following the typical procedure for **4a** using acetylene **2** (0.254 g, 2 mmol), pyrrole-2-carbaldehyde **3c** (0.227 g, 1 mmol), and 1-methyl-1*H*-imidazole (**1**, 0.082 g, 1 mmol) in MeCN (0.75 mL) at 20–25 °C for 26 h gave **4c** as a dark orange oil; yield: 0.123 g (45%). Initial pyrrole-2-carbaldehyde **3c** was recovered (0.117 g, conversion was 49%).

IR (microlayer): 1023, 1057, 1078, 1116 (C–O–C), 1641 (C=C), 2216 cm^{-1} (CN).

^1H NMR (400.13 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 5.06 (s, 1 H, H11), 5.14 (d, $^3J_{HB,HX}$ = 15.7 Hz, 1 H, H_B), 5.37 (d, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_A), 5.98 (s, 1 H, H6), 6.14 (d, 1 H, H3′), 6.19 (d, $^3J_{H4',H3'}$ = 3.9 Hz, 1 H, H4′), 6.87 (s, 1 H, H5), 7.09 (s, 1 H, H4), 7.11 (2 d, $^3J_{HB,HX}$ = 15.7 Hz, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_X), 6.76–6.89, 7.10–7.40 (m, 14 H, 3 Ph).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 33.0 (NCH_3), 34.7 (C6), 55.1 (OCH_3), 83.5 (C11), 101.4 (C7), 109.2 (N1′-CH_AH_B), 111.2 (C3′), 112.2 (C4′), 113.6 (C5′-*m*-C_{Ph}), 115.1 (13-CN), 117.0 (12-CN), 121.7 (C5), 125.5 (C2′), 126.4 (C8-*o*-C_{Ph}), 127.6 (C4), 128.1 (C10-*o*-C_{Ph}; C8-*p*-C_{Ph}), 128.6 (C10-*m*-C_{Ph}), 128.8 (C8-*m*-C_{Ph}), 130.0 (C10-*p*-C_{Ph}, C5′-*o*-C_{Ph}), 130.6 (C5′-*i*-C_{Ph}), 130.7 (C5′), 131.2 (N1′-CH_X), 131.5 (C10-*i*-C_{Ph}), 131.7 (C8-*i*-C_{Ph}), 144.7 (C2), 158.5 (C5′-*p*-C_{Ph}), 162.2 (C8), 168.3 (C10).

Anal. Calcd for $C_{36}H_{29}N_5O_2$: C, 76.71; H, 5.19; N, 12.42. Found: C, 76.58; H, 5.19; N, 12.01.

(*Z*)-3-{[(*Z*)-2-Cyano-1-phenylvinyl]oxy}-2-[(1-methyl-1*H*-imidazol-2-yl)(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)methyl]-3-phenylprop-2-enenitrile (4d)

Following the typical procedure for **4a** using acetylene **2** (0.254 g, 2 mmol), pyrrole-2-carbaldehyde **3d** (0.175 g, 1 mmol), and 1-methyl-1*H*-imidazole (**1**, 0.082 g, 1 mmol) in MeCN (0.2 mL) at 20–25 °C for 24 h) gave **4d** as a brown oil; yield: 0.030 g (14%). Initial pyrrole-2-carbaldehyde **3d** was recovered (0.102 g, conversion was 42%).

IR (microlayer): 1028, 1060, 1077, 1112, 1131 (C–O–C), 1650 (C=C), 2219 cm^{-1} (CN).

^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.76 (m, 4 H, H5′, H6′), 2.51 (m, 2 H, H4′), 2.68 (m, 2 H, H7′), 3.51 (s, 3 H, NCH_3), 5.04 (d, $^3J_{HB,HX}$ = 15.7 Hz, 1 H, H_B), 5.07 (s, 1 H, H11), 5.12 (d, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_A), 5.86 (s, 1 H, H3′), 5.88 (s, 1 H, H6), 6.86 (s, 1 H, H5), 6.88 (2 d, $^3J_{HB,HX}$ = 15.7 Hz, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_X), 7.10 (s, 1 H, H4), 7.10–7.33 (m, 10 H, 2 Ph).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 22.8 (C5′, C6′), 23.6 (C4′), 24.0 (C7′), 33.2 (NCH_3), 35.0 (C6), 83.6 (C11), 101.7 (C7), 106.6 (N1′-CH_AH_B), 110.1 (C3′), 115.1 (13-CN), 117.1 (12-CN), 119.0 (C9′), 121.8 (C5), 124.2 (C8′), 125.3 (C2′), 126.7 (C8-*o*-C_{Ph}), 127.9 (C4), 128.4 (C10-*o*-C_{Ph}), 128.9 (C8-*m*-C_{Ph}, C10-*m*-C_{Ph}, C8-*p*-C_{Ph}), 129.1 (C10-*p*-C_{Ph}), 130.0 (N1′-CH_X), 130.8 (C10-*i*-C_{Ph}), 131.7 (C8-*i*-C_{Ph}), 144.8 (C2), 162.2 (C8), 168.6 (C10).

Anal. Calcd for $C_{33}H_{29}N_5O$: C, 77.47; H, 5.71; N, 13.69. Found: C, 77.95; H, 5.68; N, 13.22.

(*Z*)-3-{[(*Z*)-2-Cyano-1-phenylvinyl]oxy}-2-[(1-methyl-1*H*-imidazol-2-yl)(1-vinyl-4,5-dihydro-1*H*-benzo[*g*]indol-2-yl)methyl]-3-phenylprop-2-enenitrile (4e)

Following the typical procedure for **4a** using acetylene **2** (0.254 g, 2 mmol), pyrrole-2-carbaldehyde **3e** (0.223 g, 1 mmol), and 1-methyl-1*H*-imidazole (**1**; 0.082 g, 1 mmol) in MeCN (2 mL) at 20–25 °C for 72 h gave **4e** as a brown oil; yield: 0.141 g (43%). Initial pyrrole-2-carbaldehyde **3e** was recovered (0.092 g, conversion was 41%).

IR (microlayer): 1028, 1077, 1113 (C–O–C), 1640 (C=C), 2219 cm^{-1} (CN).

^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.57 (m, 2 H, H4′), 2.82 (m, 2 H, H5′), 3.48 (s, 3 H, NCH_3), 5.04 (s, 1 H, H11), 5.40 (d, $^3J_{HB,HX}$ = 15.7 Hz, 1 H, H_B), 5.63 (d, $^3J_{HA,HX}$ = 8.8 Hz, 1 H, H_A), 5.96 (s, 1 H, H6), 6.03 (s, 1 H, H3′), 6.88 (s, 1 H, H5), 7.09 (s, 1 H, H4), 7.00–7.40 (m, 15 H, H6′, H7′, H8′, H9′, H_X, 2 Ph).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 22.2 (C4′), 30.5 (C5′), 33.0 (NCH_3), 34.3 (C6), 83.5 (C11), 101.4 (C7), 109.9 (N1′-CH_AH_B), 114.1 (C3′), 115.1 (13-CN), 117.0 (12-CN), 121.5 (C5), 121.7 (C9′), 124.9 (C5′-*C*3a), 126.1 (C2′, C8-*o*-C_{Ph}), 126.4 (C8′), 127.7 (C4), 128.2 (C8-*p*-C_{Ph}, C10-*o*-C_{Ph}, C7′, C9a′, C6′), 128.6 (C10-*m*-C_{Ph}), 128.8 (C8-*m*-C_{Ph}), 130.6 (N1′-CH_X), 130.7 (C10-*p*-C_{Ph}), 131.5 (C10-*i*-C_{Ph}), 131.7 (C8-*i*-C_{Ph}), 132.1 (C9b′), 136.0 (C5a′), 144.7 (C2), 162.2 (C8), 168.4 (C10).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{29}N_5O$: 559.23; found: 559.15.

Anal. Calcd for $C_{37}H_{29}N_5O$: C, 79.41; H, 5.22; N, 12.51. Found: C, 79.33; H, 5.20; N, 12.78.

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