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C2-Functionalization of 1-Substituted Imidazoles with Aldehydes and Electron-Deficient Acetylenes: A Novel Three-Component Reaction

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A novel three-component reaction between 1-substituted imidazoles, aldehydes, and electron-deficient acetylenes proceeds under mild conditions (20–25 °C, no catalyst, no solvent) to form an unknown family of C2-functionalized imidazoles in up to 74 % yield, the function constituting a push–pull combination of enol ether and acrylic moieties. In the case of cyanophenylacetylene, the function is built up stereospecifically to have the (Z) configuration. The interaction presumably occurs via zwitterion and carbene intermediates. The results contribute to basic imidazole and acetylene chemistry and open a shortcut to promising drug candidates.

Introduction

The imidazole ring is a frequent structural unit found in numerous natural products and biologically active compounds. Therefore, the search for new methods of functionalization of the imidazole nucleus, particularly C2-alkylation is considered as a standing challenge in organic synthesis.[1] Commonly, C2-alkylation of the imidazole ring starts with lithiation followed by reaction with electrophiles.[1a,2] Some 2-substituted imidazoles have been synthesized from 1-alkyl-2-trialkylstannylimidazoles and electrophiles, the former being prepared from the corresponding derivative.[1b,3] 2-Acylimidazoles have been prepared from 1-alkylimidazoles and acyl halides in the presence of amines, the corresponding imidazolium ylides being suggested as the reaction intermediates.[1d,4] Later, imidazolium ylides were reported to react with various electrophiles to yield C2-substituted imidazoles.[5] To introduce substituents at the C2 position of imidazoles, palladium- and copper-catalyzed[6] cross-couplings were employed; for example, 1-arylimidazole was treated with bromobenzene in the presence of palladium complexes to deliver 2-phenylimidazoles.[6c] In the presence of $[Ir_4(CO)_{12}]$ and diethylmethylsilane, 1-methylimidazole was treated (boiling toluene) with *n*-hexanal to afford 2-[1-(diethylmethylsiloxy)hexyl]-1-methyl-1*H*-imidazole in 35% yield.[7] Nair et al.[8] published interesting results on multicomponent interactions of imidazole carbenes with dimethylacetylenedicarboxylate and aldehydes to furnish dihydroimidazoles bridged (through the double bond) by their C2 position with a functionalized dihydrofuranone moiety.

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Recently, we reported the unprecedented direct C2-vinylation[9a,9b] and 1,3-butadienylation[9c] of 1-substituted imidazoles with cyanophenylacetylene that proceeds via zwitterionic and carbene intermediates involving N3→C2 migration of the functionalized vinyl or 1,3-butadienyl moieties. Because cyanophenylacetylene is readily available from bromophenylacetylene and copper cyanide,[10] these reactions are of general character and significantly contribute to the chemistry and application of 2-functionalized imidazoles. To extend these findings, we tried to capture the intermediate zwitterions generated from 1-substituted imidazole and electron-withdrawing acetylenes by an appropriate electrophile as a third component.

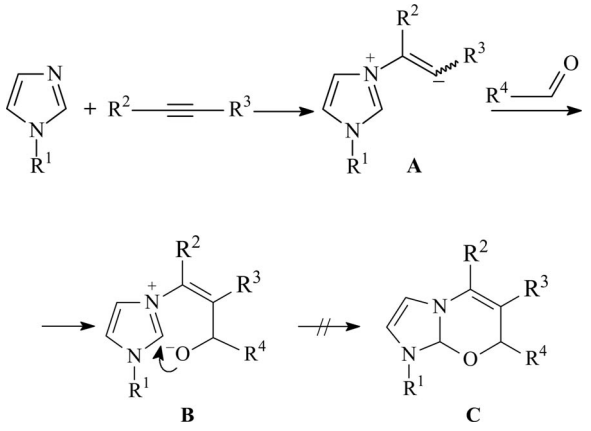
Results and Discussion

In this paper, we report on a new three-component reaction between 1-substituted imidazoles **1a**–**e**, electron-deficient acetylenes **2a**,**b**, and aldehydes **3a**–**d**, which leads to a novel class of imidazoles substituted at the C2 position with a function built up from enol ether and acrylic moieties.

On the basis of experimental data[9] indicating the formation of intermediate zwitterion **A** from 1-substitutted imidazoles and electron-withdrawing acetylenes, we expected that in the presence of aldehydes the reaction sequence depicted in Scheme 1 should take place.

As follows from Scheme 1, zwitterion **A** is to be captured by aldehydes to give zwitterion **B**, which then undergoes ring closure at the 2-position to furnish imidazo-1,3-oxazine **C**.

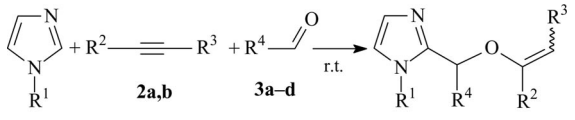
In reality, the above three components (**1a**–**e**, **2a**,**b**, and **3a**–**d**) reacted together in another, entirely unpredictable way: instead of imidazo-1,3-oxazine **C**, imidazoles substi-



Scheme 1. The expected products of the three-component reaction between 1-substitutted imidazoles, electron-withdrawing acetylenes, and aldehydes.

tuted at the 2-position with functionalized ethenyl moieties **4a**–**n** were isolated in 31–74% yield as the only products (Table 1).

Table 1. Formation of functionalized ethenyl moieties **4a**–**n** from 1-substituted imidazoles **1**, electron-deficient acetylenes **2**, and aldehydes **3**.



1a–**e** **2a**,**b** **3a**–**d** **4a**–**n**

1a: R^1 = Me **1b**: R^1 = Et **1c**: R^1 = *i*Bu **1d**: R^1 = Bn **1e**: R^1 = HC=CH_2

2a: R^2 = H, R^3 = CO_2Me **2b**: R^2 = Ph, R^3 = CN

3a: R^4 = Me **3b**: R^4 = *n*Pr **3c**: R^4 = *n*Bu **3d**: R^4 = Ph

Product	R^1	R^2	R^3	R^4	Isolated yield [%]
4a	Me	H	CO_2Me	Me	41
4b	Me	H	CO_2Me	*n*Pr	53
4c	Me	H	CO_2Me	Ph	74
4d	Me	Ph	CN	Me	58
4e	Me	Ph	CN	*n*Pr	43
4f	Me	Ph	CN	*n*Bu	31
4g	Et	Ph	CN	Me	49
4h	Et	Ph	CN	*n*Pr	54
4i	Et	Ph	CN	*n*Bu	54
4j	*i*Bu	Ph	CN	Me	62
4k	*i*Bu	Ph	CN	*n*Pr	59
4l	*i*Bu	Ph	CN	*n*Bu	57
4m	Bn	Ph	CN	Me	41
4n	HC=CH_2	Ph	CN	Me	62

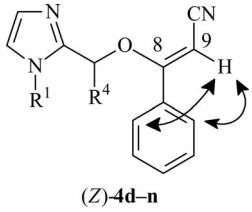
The reaction conditions are mild: room temperature and no catalyst and solvent. Duration of the reaction and the product yields depend on the structure of the reactants. For example, the reaction of imidazole **1a**, methyl propiolate (**2a**), and benzaldehyde (**3d**) was complete within 1.5 h to furnish enol ether **4c** (74% yield), whereas the reaction between the same imidazole, acetylenes **2a**,**b**, and aldehyde **3a** required 24 h to give products **4a** and **4d** (41 and 58% yield, respectively). Meanwhile, the reaction of 1-vinylimidazole (**1e**), acetylene **2b**, and aldehyde **3a** took 13 d, which results from the electron-withdrawing effect of the *N*-vinyl group that decreases the basicity at the N3 atom in imidazole **1e**.

The stereochemistry of the reaction is determined by the acetylene structure: with acetylene **2a** the function formed has both (*E*) and (*Z*) configurations (in a ratio of ca. 2–4:1), whereas in the case of acetylene **2b** the process is regio- and stereospecific to afford the (*Z*) configuration only.

Obtained enol ethers **4a**–**n** are yellow or light-brown oils soluble in conventional organic solvents. Their structures were proved by NMR (^{1}H, ^{13}C) spectroscopy by using 2D techniques (COSY, NOESY, HMBC, HSQC).

In the ^{1}H NMR spectra of enol ethers **4a**–**c**, two doublets of olefinic protons (8-H, 9-H) are observed for the (*E*) isomers at δ = 7.52–7.66 (8-H) and 5.34–5.49 (9-H) ppm and for the (*Z*) isomers at δ = 6.60–6.72 (8-H) and 4.83–4.93 (9-H) ppm. In the ^{1}H NMR spectra of enol ethers **4d**–**n**, singlets of the vinyl protons (9-H) are observed at δ = 4.91–5.09 ppm. The vinyl moiety of enol ethers **4d**–**n** manifests itself in the ^{13}C NMR spectra by signals in the region δ = 169.1–171.5 (C-8) and 75.5–78.0 (C-9) ppm. The nitrile C-atom resonates at δ = 116.2–116.9 ppm. The large difference between chemical shifts of the olefinic C-8 and C-9 carbon atoms ($\delta \approx 93$ ppm) is explained by the high polarization of the double bond caused by both the electron-withdrawing effect of the cyano group and the electron-donating p–π conjugation between the alkoxy group and the double bond common for vinyl ethers[11] (push–pull combination of the R–O and CN substituents).

According to the NOESY spectra, products **4d**–**n** are (*Z*) isomers: cross-peaks between the olefinic 9-H proton and the *ortho* protons of the phenyl groups are observed (Figure 1).



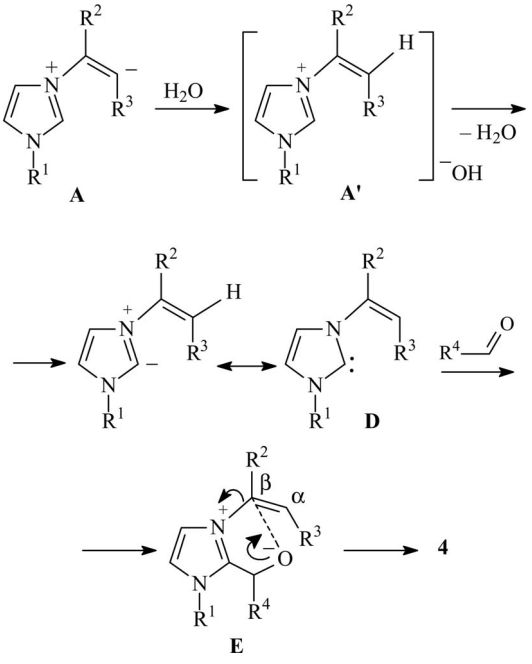
(*Z*)-**4d**–**n**

Figure 1. Cross-peaks in the 2D NOESY spectra of enol ethers **4d**–**n**.

In ^{1}H, ^{13}C and ^{15}N NMR spectra of enol ethers **4a**–**n**, the following signals of the imidazole ring are present: 4-H, 5-H; C-2, C-4, C-5; and N-1, N-3. The C-2 atom lacks protons, which confirms the location of the substituent at the 2-position of the imidazole ring. In the ^{13}C NMR spectra of compounds **4a**–**n**, the signals of C-4 and C-5 have similar values as the starting imidazoles, whereas the C-2 signal is shifted downfield (from δ = 136–137 to 143–145 ppm) by the negative inductive effect of the substituents. As expected, in the ^{15}N NMR spectra of compounds **4d**,**e**, the N-1 and N-3 nuclei resonate at different regions from δ = –223 to –225 and from δ = –120 to –129 ppm, respectively.

The IR spectra of products **4d**–**n** are in agreement with their structure: the characteristic bands of starting compounds (1713–1723 cm^{-1} for aldehyde HC=O, 2257–2275 cm^{-1} for CN in acetylene **2b**) disappear, and instead, the bands at 2214–2218 cm^{-1} belonging to the CN group at the double bond and the νC=C absorption band at 1612–1651 cm^{-1} are observed; the very strong absorption band in the region 1059–1096 cm^{-1} is attributed to the C–O–C bonds.

Apparently, zwitterion **A** reacts with traces amount of water to furnish imidazolium derivative **A′**, which is deprotonated under the action of the $^{-}$OH anion to give carbene **D**. Carbene **D** then reacts with the aldehyde to afford zwitterion **E**, which further rearranges into final products **4a**–**n** (Scheme 2).



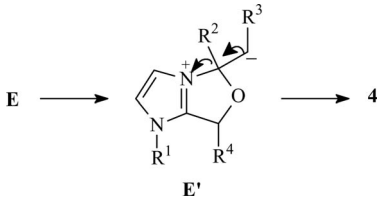
Scheme 2. Tentative reaction sequence for the formation of products **4a**–**n**.

A similar insertion of imidazoline carbene of type **D** into the C=O bond of aldehydes has been reported by Hlasta et al.[5] and Nair et al.[8]

The conversion of intermediate **E** into products **4a**–**n** involves electron-pair transfer from C_β of the acrylic moiety to N-3, accompanied by C_β–O bond formation between the emerging carbocation at the C_β carbon and the O-centered anion.

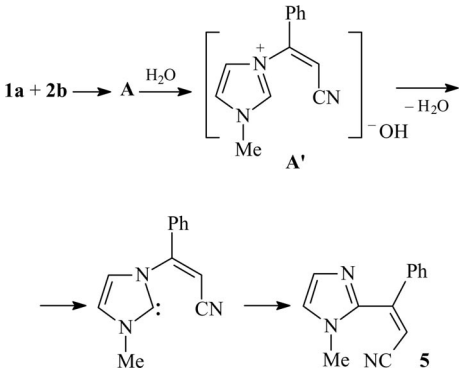
Another mode of transformation of zwitterion **E** to the final product could involve intramolecular nucleophilic addition of an oxygen anion to the electrophilic double bond to give zwitterion **E′**, which then delivers the final product by intramolecular imidazole elimination (Scheme 3).

In terms of a higher electrophilicity of some electron-deficient acetylenes over aldehydes, this route seems to be also reasonable. A shortcoming of this scheme is the necessary participation of protogenic species (e.g., water) as a catalyst, concentration of which under solvent-free conditions is negligible.



Scheme 3. Possible conversion of zwitterion **E** into product **4** by an addition–elimination sequence.

Indeed, in the presence of water, the two-component reaction of imidazole **1a** and acetylene **2b** (molar ratio **1a**/**2b**/H_2O = 1:1:4, room temperature, 24 h) delivers stereoselectively the C2-vinylation product (*Z*)-2-(2-cyano-1-phenylethenyl)-1-methylimidazole (**5**) in 30% yield (Scheme 4).



Scheme 4. Direct C2-vinylation of imidazole **1a** with acetylene **2b** in the presence of water.

A similar C2-vinylation of 1-methylimidazole with acetylene **2b** was recently reported[9a,9b] under solvent-free conditions (without special precautions against trace amounts of water). In this connection, it is worthwhile to note that in the reaction mixtures of the three-component functionalization, minor amounts (1–5%) of C2-vinylation products are always detectable (^{1}H NMR spectroscopy).

Conclusions

In summary, a facile (room temperature, noncatalytic, solvent-free), three-component reaction between 1-substituted imidazoles, electron-deficient acetylenes, and aldehydes has been discovered. The reaction leads to hitherto unknown C2-functionalized imidazoles (in up to 74% yield) functionalized with substituents representing a combination of enol ether and acrylic moieties. In the case of cyanophenylacetylene, the reaction is stereospecific to secure exclusively the (*Z*) configuration. Notably, different combinations of 1-substituted imidazoles with aldehydes obey the reaction, and such reactive functions as enol ether, acrylate,

nitrile, and styrene groups are tolerant towards the reaction conditions. The reaction has all prerequisites to occupy an important place in imidazole and acetylene chemistry, particularly for drug design.

Experimental Section

General: IR spectra were recorded with a Bruker IFS 25 instrument. NMR spectra were obtained with a Bruker DPX-400 spectrometer with HMDS as an internal standard. 1-Substituted imidazoles **1a**–**e** were prepared according to literature procedures.[12] Methyl propiolate (**2a**) is a commercial reagent ("Merck"), and cyanophenylacetylene (**2b**) was obtained by a literature procedure.[10] Column and thin-layer chromatography were carried out on neutral Al_2O_3 with chloroform/benzene/ethanol, 20:4:1 as eluent. The reaction was monitored by the disappearance of absorption bands of initial acetylenes **2a**,**b** in the reaction mixture (IR spectroscopy). For labeling of NMR assignments, see Figure 2.

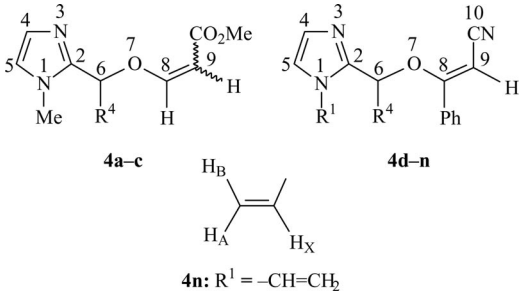


Figure 2. Labeling of hydrogen and carbon atoms in compounds **4a**–**n** used for NMR assignments.

Methyl (*E*+*Z*)-3-[1-(1-Methyl-1*H*-imidazol-2-yl)ethoxy]-2-propenoate (4a): To a mixture of methyl propiolate (**2a**; 0.084 g, 1 mmol) and ethanal (**3a**; 0.132 g, 3 mmol) was added 1-methylimidazole (**1a**; 0.082 g, 1 mmol). The mixture was stirred at 20–25 °C for 24 h. Column chromatography afforded enol ether **4a** (0.087 g, 41%) as a yellow oil. (*E*)-**4a**/(*Z*)-**4a** = 65:35. IR (microlayer): $\tilde{\nu}$ = 3576, 3396, 3138, 3112, 2990, 2952, 2891, 1714, 1644, 1623, 1497, 1438, 1416, 1380, 1330, 1284, 1221, 1194, 1139, 1117, 1067, 1042, 962, 929, 834, 757, 703, 664, 504 cm^{-1}. (*E*)-**4a**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.57 (d, $^3J_{H8,H9}$ = 12.5 Hz, 1 H, 8-H), 6.95 (s, 1 H, 4-H), 6.87 (s, 1 H, 5-H), 5.36 (d, 1 H, 9-H), 5.26 (q, $^3J_{H6,CH_3}$ = 6.7 Hz, 1 H, 6-H), 3.65 (s, 3 H, N-CH_3), 3.63 (s, 3 H, O-CH_3), 1.74 (d, 3 H, C_6-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.8 (C=O), 159.9 (C-8), 144.9 (C-2), 127.5 (C-4), 122.7 (C-5), 98.7 (C-9), 73.0 (C-6), 51.0 (O-*C*H_3), 32.9 (N-*C*H_3), 18.4 (C_6-*C*H_3) ppm. (*Z*)-**4a**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.93 (s, 1 H, 4-H), 6.88 (s, 1 H, 5-H), 6.60 (d, $^3J_{H8,H9}$ = 7.0 Hz, 1 H, 8-H), 5.33 (q, $^3J_{H6,CH_3}$ = 6.7 Hz, 1 H, 6-H), 4.85 (d, 1 H, 9-H), 3.65 (s, 3 H, O-CH_3), 3.64 (s, 3 H, N-CH_3), 1.76 (d, 3 H, C_6-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 165.2 (C=O), 155.5 (C-8), 144.7 (C-2), 127.2 (C-4), 123.0 (C-5), 97.2 (C-9), 74.9 (C-6), 50.7 (O-*C*H_3), 33.1 (N-*C*H_3), 18.5 (C_6-*C*H_3) ppm. $C_{10}H_{14}N_2O_3$ (210.23): calcd. C 57.13, H 6.71, N 13.32; found C 56.82, H 6.45, N 13.00.

Methyl (*E*+*Z*)-3-[1-(1-Methyl-1*H*-imidazol-2-yl)butoxy]-2-propenoate (4b): Analogously, from methyl propiolate (**2a**; 0.084 g, 1 mmol), *n*-butanal (**3b**; 0.072 g, 1 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (20–25 °C, 4 h) enol ether **4b** (0.126 g, 53%) was obtained as a yellow oil. (*E*)-**4b**/(*Z*)-**4b** = 75:25. IR (microlayer): $\tilde{\nu}$ = 3569, 3404, 3136, 3110, 2960, 2875, 1714, 1643, 1624, 1495, 1438, 1415, 1330, 1284, 1232, 1192, 1139, 1060, 1028, 957, 838, 802, 755, 729, 661 cm^{-1}. (*E*)-**4b**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.52 (d, $^3J_{H8,H9}$ = 12.5 Hz, 1 H, 8-H), 6.95 (s, 1 H, 4-H), 6.86 (s, 1 H, 5-H), 5.34 (d, 1 H, 9-H), 5.10 (t, $^3J_{H6,CH_2}$ = 6.7 Hz, 1 H, 6-H), 3.68 (s, 3 H, O-CH_3), 3.66 (s, 3 H, N-CH_3), 2.09–2.01 (m, 2 H, C_6-CH_2-), 1.47–1.44 (m, 2 H, C_6-CH$_2$-CH_2-), 0.95–0.92 (m, 3 H, C_6-CH$_2$-CH$_2$-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.6 (C=O), 160.1 (C-8), 144.3 (C-2), 127.3 (C-4), 122.5 (C-5), 98.4 (C-9), 77.3 (C-6), 50.7 (O-*C*H_3), 34.9 (N-*C*H_3), 32.8 (C_6-*C*H_2-), 18.4 (C_6-CH$_2$-CH$_2$-*C*H_3), 13.3 (C_6-CH$_2$-*C*H_2-) ppm. (*Z*)-**4b**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.91 (s, 1 H, 4-H), 6.79 (s, 1 H, 5-H), 6.60 (d, $^3J_{H8,H9}$ = 7.0 Hz, 1 H, 8-H), 5.13 (t, $^3J_{H6,CH_2}$ = 6.7 Hz, 1 H, 6-H), 4.83 (d, 1 H, 9-H), 3.64 (s, 3 H, N-CH_3), 3.64 (s, 3 H, O-CH_3), 2.09–2.01 (m, 2 H, C_6-CH_2-), 1.47–1.44 (m, 2 H, C_6-CH$_2$-CH_2-), 0.95–0.92 (m, 3 H, C_6-CH$_2$-CH$_2$-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 165.1 (C=O), 156.1 (C-8), 144.5 (C-2), 127.0 (C-4), 122.8 (C-5), 96.6 (C-9), 79.3 (C-6), 50.7 (O-*C*H_3), 34.9 (N-*C*H_3), 32.8 (C_6-*C*H_2-), 18.4 (C_6-CH$_2$-CH$_2$-*C*H_3), 13.3 (C_6-CH$_2$-*C*H_2-) ppm. $C_{12}H_{18}N_2O_3$ (238.28): calcd. C 60.49, H 7.61, N 11.76; found C 60.03, H 7.32, N 11.25.

Methyl (*E*+*Z*)-3-[(1-Methyl-1*H*-imidazol-2-yl)(phenyl)methoxy]-2-propenoate (4c): Analogously, from methyl propiolate (**2a**; 0.084 g, 1 mmol), benzaldehyde (**3d**; 0.106 g, 1 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (20–25 °C, 1.5 h) enol ether **4c** (0.202 g, 74%) was obtained as a yellow oil. (*E*)-**4c**/(*Z*)-**4c** = 80:20. IR (microlayer): $\tilde{\nu}$ = 3532, 3386, 3138, 3111, 3065, 3029, 2997, 2952, 2848, 1713, 1645, 1625, 1496, 1453, 1438, 1414, 1333, 1310, 1282, 1192, 1177, 1135, 1080, 1049, 1030, 1002, 968, 913, 839, 804, 755, 732, 698, 667, 640, 523 cm^{-1}. (*E*)-**4c**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 5 H, Ph), 7.66 (d, $^3J_{H8,H9}$ = 12.5 Hz, 1 H, 8-H), 6.95 (s, 1 H, 4-H), 6.81 (s, 1 H, 5-H), 6.27 (s, 1 H, 6-H), 5.49 (d, 1 H, 9-H), 3.57 (s, 3 H, O-CH_3), 3.37 (s, 3 H, N-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.0 (C=O), 160.0 (C-8), 143.6 (C-2), 135.8 (C_i, Ph), 128.2 (C_m, Ph), 127.9 (C_p, Ph), 127.2 (C-4), 125.5 (C_o, Ph), 122.7 (C-5), 99.0 (C-9), 78.2 (C-6), 50.5 (O-*C*H_3), 32.7 (N-*C*H_3) ppm. (*Z*)-**4c**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 5 H, Ph), 6.93 (s, 1 H, 4-H), 6.80 (s, 1 H, 5-H), 6.72 (d, $^3J_{H8,H9}$ = 7.0 Hz, 1 H, 8-H), 6.27 (s, 1 H, 6-H), 4.93 (d, 1 H, 9-H), 3.65 (s, 3 H, O-CH_3), 3.44 (s, 3 H, N-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 164.7 (C=O), 156.4 (C-8), 144.1 (C-2), 136.2 (C_i, Ph), 128.2 (C_m, Ph), 127.7 (C_p, Ph), 126.8 (C-4), 125.2 (C_o, Ph), 123.1 (C-5), 97.2 (C-9), 80.8 (C-6), 50.3 (O-*C*H_3), 32.8 (N-*C*H_3) ppm. $C_{15}H_{16}N_2O_3$ (272.30): calcd. C 66.16, H 5.92, N 10.29; found C 65.84, H 5.70, N 9.99.

(*Z*)-3-[(1-Methyl-1*H*-imidazol-2-yl)ethoxy]-3-phenyl-2-propenenitrile (4d): Analogously, from acetylene **2b** (0.127 g, 1 mmol), ethanal (**3a**; 0.132 g, 3 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (20–25 °C, 24 h) enol ether **4d** (0.148 g, 58%) was obtained as a light-brown oil. IR (microlayer): $\tilde{\nu}$ = 3066, 2987, 2937, 2215, 1614, 1575, 1493, 1448, 1413, 1377, 1346, 1307, 1283, 1258, 1186, 1150, 1114, 1085, 1063, 1041, 1026, 1009, 979, 920, 897, 848, 762, 698, 665, 519 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H, Ph), 6.95 (s, 1 H, 4-H), 6.88 (s, 1 H, 5-H), 5.85 (q, $^3J_{H6,CH_3}$ = 6.4 Hz, 1 H, 6-H), 5.02 (s, 1 H, 9-H), 3.83 (s, 3 H, N-CH_3), 1.77 (s, 3 H, C_6-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 170.5 (C-8), 145.3 (C-2), 133.1 (C_i, Ph), 131.5 (C_p, Ph), 129.0 (C_m, Ph) 127.7 (C-4), 127.1 (C_o, Ph), 122.9 (C-5), 116.8 (C-10, *C*N), 77.1 (C-9), 73.0 (C-6), 43.6 (N-*C*H_3), 19.1 (C_6-*C*H_3) ppm. ^{15}N NMR (40.55 MHz, $CDCl_3$): δ = –124.7 (C*N*-10), –129.4 (N-3), –224.9 (N-1) ppm. $C_{15}H_{15}N_3O$ (253.30): calcd. C 71.13, H 5.97, N 16.59; found C 71.40, H 5.80, N 16.85.

(*Z*)-3-[(1-Methyl-1*H*-imidazol-2-yl)butoxy]-3-phenyl-2-propenenitrile (4e): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-but-

anal (**3b**; 0.072 g, 1 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (20–25 °C, 24 h) enol ether **4e** (0.122 g, 43%) was obtained as a yellow oil. IR (microlayer): ṽ = 3065, 3034, 2962, 2935, 2874, 2216, 1612, 1576, 1493, 1463, 1448, 1324, 1283, 1250, 1184, 1121, 1087, 1057, 1027, 988, 922, 760, 698, 662, 525 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H, Ph), 6.92 (s, 1 H, 4-H), 6.85 (s, 1 H, 5-H), 5.57 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 4.93 (s, 1 H, 9-H), 3.77 (s, 3 H, N-CH_3), 2.10 (m, 2 H, C_6-CH_2-), 1.40–1.26 (m, 2 H, C_6-CH$_2$-CH_2-), 0.88 [t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C_6-$(CH_2)_2$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 171.5 (C-8), 144.7 (C-2), 134.0 (C_i, Ph), 131.4 (C_p, Ph), 129.1 (C_m, Ph), 127.8 (C-4), 127.3 (C_o, Ph), 122.8 (C-5), 116.8 (C-10, *C*N), 78.0 (C-9), 77.1 (C-6), 36.0 (C_6-*C*H$_2$-), 33.8 (N-*C*H$_3$), 18.7 (C_6-CH$_2$-*C*H$_2$-), 13.8 [C_6-$(CH_2)_2$-*C*H$_3$] ppm. ^{15}N NMR (40.55 MHz, $CDCl_3$): δ = –120.0 (N-3), –125.1 (C*N*-10), –222.9 (N-1) ppm. $C_{17}H_{19}N_3O$ (281.36): calcd. C 72.57, H 6.81, N 14.91; found C 72.05, H 6.80, N 14.45.

(*Z*)-3-{[(1-Methyl-1*H*-imidazol-2-yl)pentyl]oxy}-3-phenyl-2-propenenitrile (4f): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-pentanal (**3c**; 0.086 g, 1 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (20–25 °C, 24 h) enol ether **4f** (0.091 g, 31%) was obtained as a yellow oil. IR (microlayer): ṽ = 3064, 2958, 2932, 2872, 2216, 1612, 1576, 1493, 1466, 1448, 1413, 1330, 1282, 1248, 1183, 1088, 1028, 992, 919, 760, 699, 661, 525 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H, Ph), 6.83 (s, 1 H, 4-H), 6.76 (s, 1 H, 5-H), 5.58 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 4.91 (s, 1 H, 9-H), 3.79 (s, 3 H, N-CH_3), 2.25–2.12 (m, 2 H, C_6-CH_2-), 1.36–1.18 [m, 4 H, C_6-CH$_2$-(CH_2)$_2$-], 0.83 [t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C_6-$(CH_2)_3$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 171.2 (C-8), 144.5 (C-2), 132.9 (C_i, Ph), 131.3 (C_p, Ph), 128.9 (C_m, Ph), 127.7 (C-4), 127.2 (C_o, Ph), 122.7 (C-5), 116.7 (C-10, *C*N), 77.8 (C-9), 77.0 (C-6), 33.5 (N-*C*H$_3$), 33.5 (C_6-*C*H$_2$-), 27.2 (C_6-CH$_2$-*C*H$_2$-), 22.3 [C_6-$(CH_2)_2$-*C*H$_2$-], 13.8 [C_6-$(CH_2)_3$-*C*H$_3$] ppm. $C_{18}H_{20}N_3O$ (295.38): calcd. C 73.19, H 7.17, N 14.23; found C 73.17, H 7.08, N 14.13.

(*Z*)-3-[(1-Ethyl-1*H*-imidazol-2-yl)ethoxy]-3-phenyl-2-propenenitrile (4g): Analogously, from acetylene **2b** (0.127 g, 1 mmol), ethanal (**3a**; 0.132 g, 3 mmol), and 1-ethylimidazole (**1b**; 0.096 g, 1 mmol) (20–25 °C, 24 h) enol ether **4g** (0.132 g, 49%) was obtained as a light-brown oil. IR (microlayer): ṽ = 3066, 2984, 2938, 2214, 1651, 1606, 1569, 1492, 1465, 1448, 1378, 1347, 1305, 1286, 1257, 1183, 1150, 1114, 1088, 1059, 1025, 963, 920, 896, 850, 760, 697, 666, 521 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.60–7.40 (m, 5 H, Ph), 6.97 (s, 1 H, 4-H), 6.92 (s, 1 H, 5-H), 5.92 (q, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 5.03 (s, 1 H, 9-H), 4.14 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, N-CH_2-), 1.76 (s, 3 H, C_6-CH_3), 1.38 (t, 3 H, N-CH$_2$-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 169.8 (C-8), 144.4 (C-2), 132.8 (C_i, Ph), 131.1 (C_p, Ph), 128.5 (C_m, Ph), 127.6 (C-4), 126.6 (C_o, Ph), 120.1 (C-5), 116.4 (C-10, *C*N), 76.6 (C-9), 72.1 (C-6), 40.8 (N-*C*H$_2$-), 18.7 (C_6-*C*H$_3$), 16.1 (N-CH$_2$-*C*H$_3$) ppm. $C_{16}H_{17}N_3O$ (267.33): calcd. C 71.89, H 6.41, N 15.72; found C 71.40, H 6.31, N 15.74.

(*Z*)-3-[(1-Ethyl-1*H*-imidazol-2-yl)butoxy]-3-phenyl-2-propenenitrile (4h): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-butanal (**3b**; 0.072 g, 1 mmol), and 1-ethylimidazole (**1b**; 0.096 g, 1 mmol) (20–25 °C, 24 h) enol ether **4h** (0.160 g, 54%) was obtained as a yellow oil. IR (microlayer): ṽ = 3064, 2963, 2930, 2874, 2855, 2218, 1612, 1575, 1492, 1448, 1406, 1379, 1280, 1260, 1178, 1160, 1101, 1027, 965, 918, 760, 695 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H, Ph), 6.98 (s, 1 H, 4-H), 6.93 (s, 1 H, 5-H), 5.67 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 4.93 (s, 1 H, 9-H), 4.20 (q, $^3J_{H,H}$ = 6.8 Hz, 2 H, N-CH_2-), 2.25–2.12 (m, 2 H, C_6-CH_2-), 1.43–1.25 (m, 2 H, C_6-CH$_2$-CH_2-), 1.36 (t, 3 H, N-CH$_2$-CH_3), 0.88 [t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C_6-$(CH_2)_2$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 171.2 (C-8), 143.9 (C-2), 133.8 (C_i, Ph), 131.1 (C_p, Ph), 128.9 (C_m, Ph), 127.7 (C-4), 127.0 (C_o, Ph), 119.9 (C-5), 116.7 (C-10, *C*N), 77.9 (C-9), 77.1 (C-6), 40.6 (N-*C*H$_2$-), 35.4 (C_6-*C*H$_2$-), 18.6 (C_6-CH$_2$-*C*H$_2$-), 16.3 (N-CH$_2$-*C*H$_3$), 13.5 [C_6-$(CH)_2$-*C*H$_3$] ppm. $C_{18}H_{21}N_3O$ (295.38): calcd. C 73.19, H 7.17, N 14.23; found C 72.75, H 6.90, N 14.45.

(*Z*)-3-{[(1-Ethyl-1*H*-imidazol-2-yl)pentyl]oxy}-3-phenyl-2-propenenitrile (4i): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-pentanal (**3c**; 0.086 g, 1 mmol), and 1-ethylimidazole (**1b**; 0.096 g, 1 mmol) (20–25 °C, 24 h) enol ether **4i** (0.166 g, 54%) was obtained as a light-brown oil. IR (microlayer): ṽ = 3065, 2958, 2933, 2872, 2216, 1608, 1576, 1492, 1466, 1448, 1379, 1331, 1277, 1258, 1180, 1158, 1090, 1028, 992, 919, 896, 849, 761, 697, 662, 526 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H, Ph), 6.98 (s, 1 H, 4-H), 6.93 (s, 1 H, 5-H), 5.68 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 4.94 (s, 1 H, 9-H), 4.15 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, N-CH_2-), 2.25–2.14 (m, 2 H, C_6-CH_2-), 1.39 (t, 3 H, N-CH$_2$-CH_3), 1.33–1.17 [m, 4 H, C_6-CH$_2$-(CH_2)$_2$-], 0.83 [t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C_6-$(CH_2)_3$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 170.6 (C-8), 143.6 (C-2), 132.58 (C_i, Ph), 130.9 (C_p, Ph), 128.4 (C_m, Ph), 127.7 (C-4), 126.7 (C_o, Ph), 119.7 (C-5), 116.2 (C-10, *C*N), 76.8 (C-9), 76.3 (C-6), 40.7 (N-*C*H$_2$-), 33.2 (C_6-*C*H$_2$-), 26.8 (C_6-CH$_2$-*C*H$_2$-), 21.9 [C_6-$(CH_2)_2$-*C*H$_2$-], 16.1 (N-CH$_2$-*C*H$_3$), 13.4 [C_6-$(CH_2)_3$-*C*H$_3$] ppm. $C_{19}H_{23}N_3O$ (309.41): calcd. C 73.76, H 7.49, N 13.58; found C 73.25, H 7.28, N 13.23.

(*Z*)-3-[(1-Isobutyl-1*H*-imidazol-2-yl)ethoxy]-3-phenyl-2-propenenitrile (4j): Analogously, from acetylene **2b** (0.127 g, 1 mmol), ethanal (**3a**; 0.132 g, 3 mmol), and 1-isobutylimidazole (**1c**; 0.124 g, 1 mmol) (20–25 °C, 24 h) enol ether **4j** (0.182 g, 62%) was obtained as a light-brown oil. IR (microlayer): ṽ = 3066, 2964, 2936, 2874, 2215, 1650, 1606, 1575, 1491, 1469, 1448, 1376, 1344, 1306, 1277, 1254, 1183, 1151, 1109, 1090, 1062, 1014, 978, 921, 896, 841, 762, 733, 697, 666, 533 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 5 H, Ph), 7.00 (s, 1 H, 4-H), 6.89 (s, 1 H, 5-H), 6.02 (q, $^3J_{H6,CH_3}$ = 6.4 Hz, 1 H, 6-H), 5.09 (s, 1 H, 9-H), 3.81–3.79 (m, 2 H, N-CH_2-), 2.03–1.96 (m, 1 H, N-CH$_2$-C*H*-), 1.81 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, C_6-CH_3), 0.88 [d, $^3J_{H,H}$ = 6.8 Hz, 6 H, N-CH$_2$-CH-(CH_3)$_2$] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 169.1 (C-8), 144.6 (C-2), 132.9 (C_i, Ph), 130.9 (C_p, Ph), 128.3 (C_m, Ph), 127.4 (C-4), 126.4 (C_o, Ph), 120.8 (C-5), 116.4 (C-10, *C*N), 75.5 (C-9), 70.9 (C-6), 52.9 (N-*C*H$_2$-), 29.6 (N-CH$_2$-*C*H-), 19.4 (C_6-*C*H$_3$), 18.4 [N-CH$_2$-CH-(*C*H$_3$)$_2$] ppm. $C_{18}H_{21}N_3O$ (295.38): calcd. C 73.19, H 7.17, N 14.23; found C 73.72, H 7.15, N 14.30.

(*Z*)-3-[(1-Isobutyl-1*H*-imidazol-2-yl)butoxy]-3-phenyl-2-propenenitrile (4k): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-butanal (**3b**; 0.072 g, 1 mmol), and 1-isobutylimidazole (**1c**; 0.124 g, 1 mmol) (20–25 °C, 24 h) enol ether **4k** (0.189 g, 59%) was obtained as a brown oil. IR (microlayer): ṽ = 3065, 2963, 2934, 2874, 2216, 1605, 1575, 1491, 1468, 1448, 1370, 1344, 1323, 1279, 1254, 1180, 1154, 1095, 1027, 982, 950, 932, 894, 756, 697, 663, 526 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.45–7.32 (m, 5 H, Ph), 7.01 (s, 1 H, 4-H), 6.89 (s, 1 H, 5-H), 5.81 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 5.01 (s, 1 H, 9-H), 3.83–3.80 (m, 2 H, N-CH_2-), 2.24–2.15 (m, 2 H, C_6-CH_2-), 2.04–1.97 (m, 1 H, N-CH$_2$-C*H*-), 1.44–1.26 (m, 2 H, C_6-CH$_2$-CH_2-), 0.92–0.87 [m, 9 H, N-CH$_2$-CH-(CH_3)$_2$ and C_6-$(CH_2)_2$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 170.5 (C-8), 144.4 (C-2), 133.2 (C_i, Ph), 131.3 (C_p, Ph), 128.8 (C_m, Ph), 128.0 (C-4), 127.1 (C_o, Ph), 121.1 (C-5), 116.9 (C-10, *C*N), 76.1 (C-9), 75.5 (C-6), 53.4 (N-*C*H$_2$-), 35.6 (C_6-*C*H$_2$-), 30.1 (N-CH$_2$-*C*H-), 19.8 [N-CH$_2$-CH-(*C*H$_3$)$_2$], 18.4 (C_6-CH$_2$-*C*H$_2$-), 13.8 [C_6-$(CH_2)_2$-*C*H$_3$] ppm. $C_{20}H_{25}N_3O$ (323.44): calcd. C 74.27, H 7.79, N 12.99; found C 74.42, H 7.56, N 12.86.

(*Z*)-3-{[(1-Isobutyl-1*H*-imidazol-2-yl)pentyl]oxy}-3-phenyl-2-propenenitrile (4l): Analogously, from acetylene **2b** (0.127 g, 1 mmol), *n*-pentanal (**3c**; 0.086 g, 1 mmol), and 1-isobutylimidazole (**1c**; 0.124 g, 1 mmol) (20–25 °C, 48 h) enol ether **4l** (0.193 g, 57%) was obtained as a light-brown oil. IR (microlayer): $\tilde{\nu}$ = 3066, 2960, 2932, 2873, 2216, 1605, 1575, 1520, 1492, 1468, 1448, 1391, 1370, 1331, 1312, 1276, 1254, 1180, 1155, 1096, 1044, 1029, 1001, 981, 963, 920, 896, 850, 818, 756, 697, 662, 554, 526, 506, 439 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, Ph), 7.02 (s, 1 H, 4-H), 6.89 (s, 1 H, 5-H), 5.82 (t, $^3J_{H6,CH_2}$ = 6.4 Hz, 1 H, 6-H), 5.00 (s, 1 H, 9-H), 3.86–3.83 (m, 2 H, N-CH_2-), 2.25–2.05 (m, 2 H, C_6-CH_2-), 2.04–1.99 (m, 1 H, N-CH_2-CH-), 1.32–1.26 [m, 4 H, C_6-CH_2-(CH_2)$_2$-], 0.93 [d, $^3J_{H,H}$ = 6.8 Hz, 6 H, N-CH_2-CH-(CH_3)$_2$], 0.86–0.83 [m, 3 H, C_6-$(CH_2)_3$-CH_3] ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 170.2 (C-8), 144.3 (C-2), 133.1 (C_i, Ph), 131.1 (C_p, Ph), 128.5 (C_m, Ph), 127.8 (C-4), 126.8 (C_o, Ph), 120.8 (C-5), 116.6 (C-10, *C*N), 75.6 (C-9), 75.5 (C-6), 53.2 (N-*C*H_2-), 33.1 (C_6-*C*H_2-), 29.9 (N-CH_2-*C*H-), 26.9 (C_6-CH_2-*C*H_2-), 22.2 [C_6-$(CH_2)_2$-*C*H_2-], 19.60 [N-CH_2-CH-(*C*H_3)$_2$], 13.6 [C_6-$(CH_2)_3$-*C*H_3] ppm. $C_{21}H_{27}N_3O$ (337.46): calcd. C 74.74, H 8.06, N 12.45; found C 74.32, H 7.86, N 12.36.

(*Z*)-3-[1-(1-Benzyl-1*H*-imidazol-2-yl)ethoxy]-3-phenyl-2-propenenitrile (4m): Analogously, from acetylene **2b** (0.127 g, 1 mmol), ethanal (**3a**; 0.132 g, 3 mmol), and 1-benzylimidazole (**1d**; 0.158 g, 1 mmol) in CH_3CN (1 mL) (20–25 °C, 4 d) enol ether **4m** (0.135 g, 41%) was obtained as a brown oil. IR (microlayer): $\tilde{\nu}$ = 3066, 3033, 2986, 2937, 2874, 2214, 1648, 1607, 1574, 1494, 1449, 1434, 1377, 1345, 1321, 1303, 1283, 1222, 1166, 1114, 1078, 1063, 1028, 1003, 967, 919, 897, 846, 759, 697, 664, 579, 459 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.27–7.07 (m, 10 H, 2 Ph), 7.03 (s, 1 H, 4-H), 6.88 (s, 1 H, 5-H), 5.89 (q, $^3J_{H6,CH_3}$ = 6.5 Hz, 1 H, 6-H), 5.38 (d, $^2J_{H,H}$ = 16.0 Hz, 1 H, CH_2Ph), 5.25 (d, 1 H, CH_2Ph), 4.97 (s, 1 H, 9-H), 1.68 (d, 3 H, C_6-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 169.9 (C-8), 145.3 (C-2), 136.3 (C_i, Ph in Bn), 133.1 (C_i, Ph), 131.3 (C-4), 128.8 (C_m, Ph in Bn and Ph), 128.0 (C_p, Ph in Bn), 127.9 (C_p, Ph), 126.9 (C_o, Ph in Bn and Ph), 122.0 (C-5), 116.7 (C-10, *C*N), 76.7 (C-9), 72.4 (C-6), 49.9 (N-*C*H_2-) ppm. $C_{21}H_{19}N_3O$ (329.40): calcd. C 76.57, H 5.81, N 12.76; found C 76.22, H 5.65, N 12.30.

(*Z*)-3-[1-(1-Vinyl-1*H*-imidazol-2-yl)ethoxy]-3-phenyl-2-propenenitrile (4n): Analogously, from acetylene **2b** (0.127 g, 1 mmol), ethanal (**3a**; 0.132 g, 3 mmol), and 1-vinylimidazole (**1d**; 0.094 g, 1 mmol) (20–25 °C, 13 d) enol ether **4n** (0.163 g, 62%) was obtained as a yellow oil. IR (microlayer): $\tilde{\nu}$ = 3067, 3036, 2987, 2936, 2872, 2214, 1646, 1608, 1569, 1524, 1491, 1448, 1429, 1380, 1345, 1321, 1303, 1277, 1257, 1177, 1168, 1113, 1082, 1065, 1048, 1027, 1003, 962, 894, 854, 762, 695, 670, 567 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 5 H, Ph and 1 H, H_X), 7.22 (s, 1 H, 4-H), 6.96 (s, 1 H, 5-H), 5.82 (q, $^3J_{H6,CH_3}$ = 6.6 Hz, 1 H, 6-H), 5.27 (d, $^3J_{HB,HX}$ = 15.3 Hz, 1 H, H_B), 5.02 (s, 1 H, 9-H), 4.96 (d, $^3J_{HA,HX}$ = 8.1 Hz, 1 H, H_A), 1.74 (d, 3 H, C_6-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 170.3 (C-8), 144.8 (C-2), 132.8 (C_i, Ph), 131.5 (*C*-H_X), 129.2 (C_p, Ph), 129.0 (C_m, Ph), 128.7 (C-4), 127.1 (C_o, Ph), 117.7 (C-5), 116.6 (C-10, *C*N), 104.0 (H_A-*C*-H_B), 78.4 (C-9), 72.9 (C-6), 19.5 (C_6-*C*H_3) ppm. $C_{16}H_{15}N_3O$ (265.31): calcd. C 72.43, H 5.70, N 15.84; found C 72.00, H 5.49, N 15.50.

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