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C(2)-Functionalization of 1-substituted imidazoles with cyanoacetylenes and aromatic or heteroaromatic aldehydes

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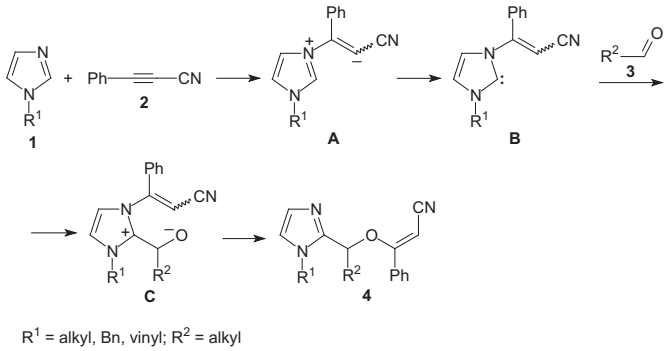
ABSTRACT

Substituted imidazoles (substituents are Me, Et, *i*-Bu, *n*-Hexyl, $(CH_2)_2S$–Bu-*n*, Ph, Bn) react smoothly (room temperature, without catalyst and solvent) with cyanoacetylenes (3-phenyl-2-propynenitrile and 4-(1-butoxyethoxy)-4-methyl-2-pentynenitrile) and aromatic or heteroaromatic aldehydes (benzaldehyde, 4-CN-benzaldehyde, pyridine-3-aldehyde) to give 3-(2-imidazolyl)-3-aryl-2-acylpropanenitriles, a hitherto unknown family of functionalized imidazole derivatives, in up to 62% yield. This three-component manifold represents a novel *C*(2)-functionalization of the imidazole nucleus involving zwitterionic, carbene and enol ether intermediates. Unlike the analogous reaction with aliphatic aldehydes, which gives enol ethers, in this case the latter undergo the further rearrangement to 3-(2-imidazolyl)-3-aryl-2-acylpropanenitriles.

1. Introduction

In recent years, growing attention has been paid to the reactions of zwitterionic adducts of neutral nucleophiles[1,2] (pyridines, quinolines, isoquinolines, quinoxalines, phenanthridines, anabazines, and the like) with electron-deficient acetylenes, e.g., dialkyl acetylene dicarboxylates,[1] α,β-acetylenic γ-hydroxy nitriles, and 3-phenyl-2-propynenitrile.[2] A special family of neutral nucleophiles, heterocyclic carbenes are capable of reacting with acetylene dicarboxylates to generate zwitterions, which are intercepted by a third component (aldehydes, ketenes, isothiocyanates) to afford a variety of valuable heterocyclic compounds.[3] Particular efforts now are focused on the exploration of these reactions for the synthesis of diverse imidazole derivatives, since the imidazole ring is a frequent structural scaffold of numerous natural products and drugs.[4]

Recently, we discovered the direct *C*(2)-vinylation[5a,b] and 1,3-butadienylation[5c] of 1-substituted imidazoles **1** with 3-phenyl-2-propynenitrile (**2**), which involves the zwitterionic and carbene intermediates. Thanks to the availability of 3-phenyl-2-propynenitrile these reactions contribute to the chemistry and exploitation of 2-functionalized imidazoles. Recently, we extended these findings by intercepting the intermediate zwitterions by aliphatic aldehydes and resulting *C*(2)-functionalized imidazoles, (*Z*)-3-(1-alkylimidazol-2-yl)alkoxy-3-phenyl-2-propenenitriles **4**, being isolated in up to 62% yield (Scheme 1).[6] Here, it should be emphasized that only aliphatic aldehydes were used. The reaction is rationalized as proceeding through the formation of the intermediate carbene **B** (via proton transfer from position 2 of the imidazole ring to the carbanionic center of the zwitterion **A**), which then is added to the C=O



R^1 = alkyl, Bn, vinyl; R^2 = alkyl

Scheme 1. The formation of (*Z*)-3-(1-alkylimidazol-2-yl)alkoxy-3-phenyl-2-propenenitriles **4** from the zwitterion **A**, carbene **B**, and aliphatic aldehyde.[6]

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bond of the aldehyde to deliver the zwitterion **C**, rearranging to final product **4** (Scheme 1).[6]

Herein we report on the reaction of 1-substituted imidazoles with cyanoacetylenes and aromatic or heteroaromatic aldehydes, which against expectations undergoes a further rearrangement to end up with a different *C*(2)-functionalization of the imidazole ring.

2. Results and discussion

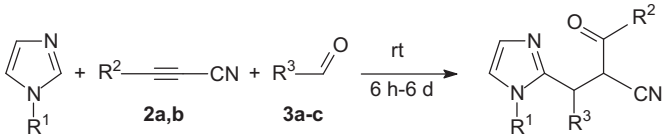
When 1-substituted imidazoles **1a**–**g** and cyanoacetylenes **2a**,**b** were allowed to react (room temperature, without solvent and catalysts, 6 h–6 days) with aromatic or heteroaromatic aldehydes **3a**–**c**, none of the expected enol ethers **4** were isolated (Scheme 1) except for one special case (vide infra). Instead, 3-(2-imidazolyl)-3-aryl(hetaryl)-2-acylpropanenitriles **5a**–**j** were isolated as the only products in 17–62% yields (Table 1).

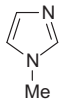
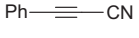
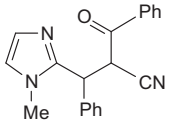
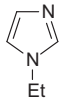
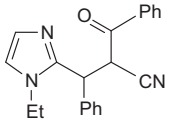
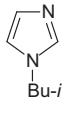
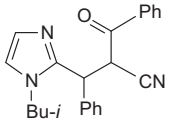
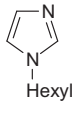
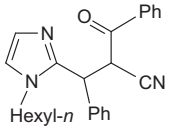
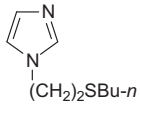
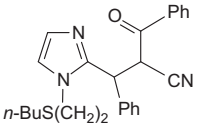
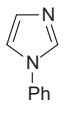
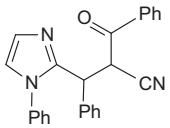
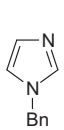
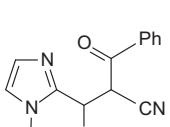
The structures of propanenitriles **5a**–**j** have been unambiguously assigned by the X-ray analysis of single crystals of products **5a**,**g**,**h** (Figs. 1–3) and confirmed by ^{1}H, ^{13}C, ^{15}N NMR, 2D (NOESY, COSY, HMBC, HSQC), and IR spectroscopy.

The presence of the 4-cyanophenyl substituent at the C-6 of compound **5h** (Fig. 4) is confirmed by the appearance of a cross-peak caused by the correlation of H-6 proton signal (4.95 ppm) with C-11 and C-15 carbon signals (129.6 ppm) over three bonds in the HMBC spectra (the same picture is observed for compound **5i**).

In the ^{1}H NMR spectra of propanenitriles **5**, splitting of the signals assigned to H-6 and H-7 (Fig. 4) proton signals is observed in the region 4.77–4.99 and 5.64–5.77 ppm, respectively, thus indicating the existence of compounds **5** as mixtures of two diastereomers (in a ratio of 10:1.6–2.5). In the IR spectra of propanenitriles **5**, the carbonyl group absorption bands appears in the region 1690–1704 cm^{-1} and the broad, low intensity bands attributable to the CN group at an

Table 1
Three-component reaction of imidazole, cyanoacetylene, and aromatic or heteroaromatic aldehydes: a new *C*(2)-functionalization of the imidazole ring



Imidazole		Cyanoacetylene		Aldehyde		Functionalized imidazole		Isolated yield (%)
	**1a**		**2a**		**3a**		**5a**	54
	**1b**		**2a**		**3a**		**5b**	51
	**1c**		**2a**		**3a**		**5c**	48
	**1d**		**2a**		**3a**		**5d**	52
	**1e**		**2a**		**3a**		**5e**	36
	**1f**		**2a**		**3a**		**5f**	51
	**1g**		**2a**		**3a**		**5g**	62

(*continued on next page*)

Table 1 (*continued*)

Imidazole	Cyanoacetylene	Aldehyde	Functionalized imidazole	Isolated yield (%)
1b	**2a**	4-CNPh–CHO	**3b**	**5h** 44
1a	**2a**	3-Py–CHO	**3c**	**5i** 17
1a	**2b**		**3a**	**5j** 32

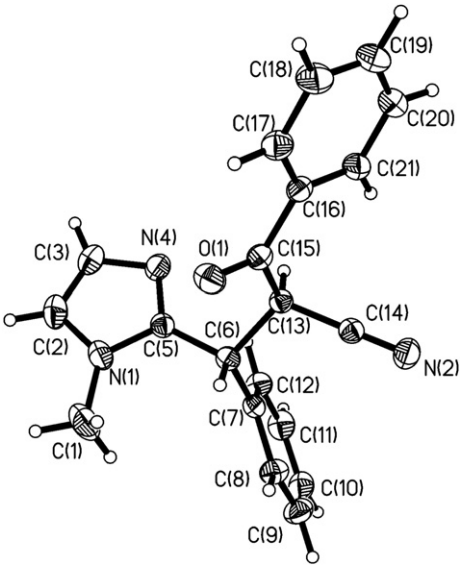


Fig. 1. ORTEP diagram of propanenitrile **5a**.

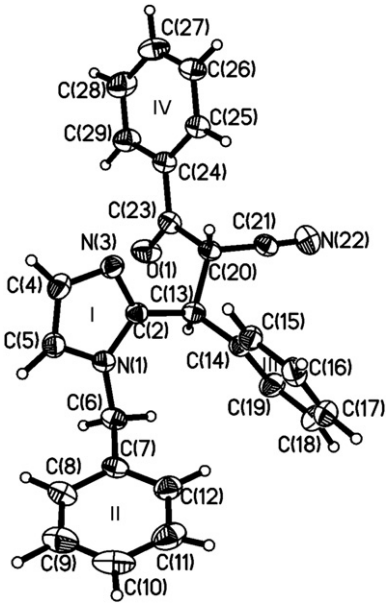


Fig. 2. ORTEP diagram of propanenitrile **5g**.

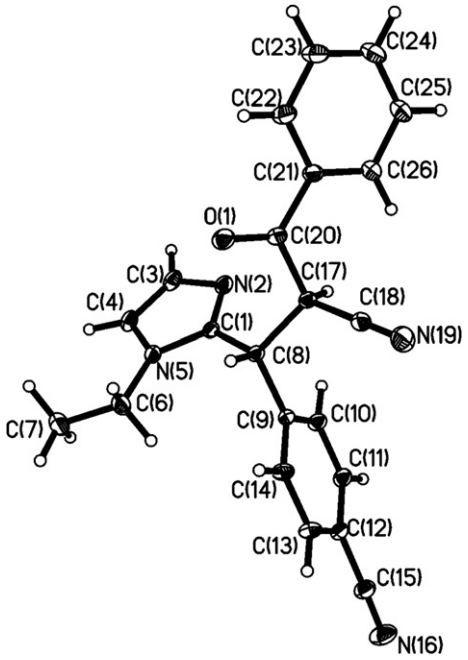


Fig. 3. ORTEP diagram of propanenitrile **5h**.

sp^3 carbon are present at 2235–2245 cm^{-1}, whereas in enol ethers **4** spectra the CN function is manifested itself as narrow intense bands at 2214–2218 cm^{-1}.[6]

Evidently, the formation of propanenitriles **5a**–**j** results from the rearrangement of the type **4** enol ethers (Scheme 2) and hence passes through all the steps designated on Scheme 1. The key intermediate of the rearrangement is carbene **B**. Its formation has been distinctly detected experimentally in ^{13}C NMR spectra ($CDCl_3$) of the reaction mixture where is always observed the characteristic signal at 223.4 ppm commonly assigned in the literature[7] to the carbene carbon.

The rearrangement (Scheme 2) is triggered by the cleavage of the ether C_6–O bond with the electron pairs transfer to the antibonding π-orbital of the vinyl group to induce the carbanion-like center at the carbon atom adjacent to the CN function thus weakening the C=C bond. This facilitates the *Z*/*E* isomerization of the acrylonitrile moiety and, finally, the formation of C_6–C_7 bond. In this case, the driving force of the rearrangement is the stabilization

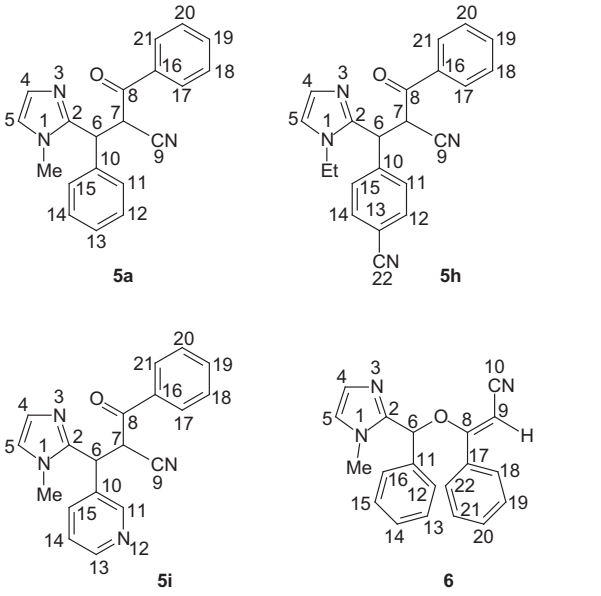
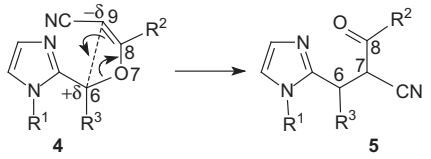


Fig. 4. Labeling of hydrogen and carbon atoms in the compounds **5a**, **5h**, **5i**, and **6** used for NMR assignments.

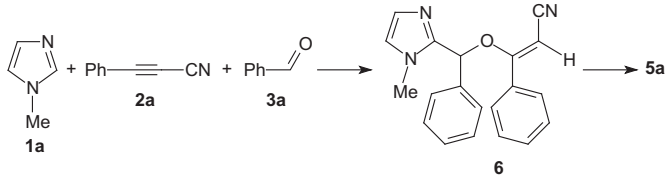


Scheme 2. The rearrangement of enol ethers **4** to propanenitriles **5**.

of the carbocation-like center at the C_6 atom by the aromatic substituent R^3 (the benzyl cation type stabilization), which does not take place with aliphatic aldehydes.

The formation of two or more [in the case of 4-(1-butoxyethoxy)-4-methyl-2-pentynenitrile (**2b**)] diastereomers indicates that the rearrangement is not fully stereoselective and hence entirely concerted (according to the data for aliphatic aldehydes,[6] the enol intermediates are of *Z*-configuration only). Meanwhile, the isolation of the expected products **5j** though in a modest yield (32%) shows that the reaction tolerates even highly sterically strained substrates.

As additional evidence of Scheme 2, in one case the expected intermediate enol ether **6** was isolated in 3% yield, which kept gradually transforming to the corresponding propanenitrile **5a** (54%, Scheme 3). Besides, enol ethers **4** previously obtained by the same three-component reaction with aliphatic aldehydes (Scheme 1), upon storage (ca. 6 months, $CDCl_3$, room temperature) completely rearrange to the corresponding propanenitriles, which also exist as a diastereomer mixture. The latter supports the argument in favor of the above-suggested non-concerted rearrangement of the enol ethers **4**. Additionally, this shows that the propanenitriles **5** are energetically more favorable compared to enol ethers **4** and **6**, which therefore are the kinetic products.



Scheme 3. Isolation of intermediate enol ether **6**.

3. Conclusions

In summary, a novel facile three-component reaction between 1-substituted imidazoles, cyanoacetylenes, and aromatic and heteroaromatic aldehydes to afford a hitherto unknown family of densely *C*(2)-functionalized imidazoles, 3-(2-imidazolyl)-3-aryl-2-acylpropanenitriles, has been found. This unusual *C*(2)-functionalization of the imidazole nucleus proceeds via the zwitterionic, carbene and enol ether intermediates. In contrast to the previously reported similar reactions with aliphatic aldehydes, the functionalization does not stop at the step of the enol ethers formation but is accomplished with the further rearrangement to 3-(2-imidazolyl)-3-aryl-2-acylpropanenitriles. This reaction significantly contributes to the basic and synthetic chemistry of imidazole, electron-deficient acetylenes, and heterocyclic zwitterions and carbenes.

4. Experimental section

4.1. General

NMR spectra were run on a Bruker DPX-400 spectrometer with HMDS as an internal standard. IR spectra were recorded on a IFS 25 instrument. 1-Substituted imidazoles **1a**–**e** were prepared according to literature procedures.[7d,8] 3-Phenyl-2-propynenitrile (**2a**) and 4-(1-butoxyethoxy)-4-methyl-2-pentynenitrile (**2b**) were synthesized as reported in protocol.[9,10] Column and thin-layer chromatography was carried out on neutral Al_2O_3 with chloroform/benzene/ethanol (20:4:1) mixture as eluent. The reaction was controlled by disappearance of spot of the initial propynenitriles **2** on fine layer of Al_2O_3.

4.2. X-ray diffraction

X-ray diffraction studies of the compounds **5a**, **5g**, and **5h** were carried out with KM-4 KUMA DIFFRACTION diffractometer, at room temperature (ω/2θ-scanning, Mo Kα radiation, graphite monochromator). Crystalline structures were solved by direct methods followed with Fourier synthesis by using SHELXS-97.[11a] All non-hydrogen atoms were refined by using anisotropic full-matrix approximation with the use of SHELXL-97.[11b] Coordinates of hydrogen atoms were defined experimentally and refined isotropically. These data are available via www.ccdc.cam.uk/contsretrieving.html (or from CCDC, 12 Union CambrigeCB2 1EZ, UK, fax: +44 (0) 1223 336 033; or e-mail:deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers CCDC 709166 (**5a**), CCDC 709167 (**5g**), CCDC 782010 (**5h**).

4.3. Preparation of 3-(2-imidazolyl)-3-aryl-2-acylpropanenitriles

*4.3.1. 2-Benzoyl-3-(1-methyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5a**).* To a mixture of cyanoacetylene **2a** (0.127 g, 1 mmol) and benzaldehyde (**3a**; 0.106 g, 1 mmol) was added on stirring 1-methylimidazole (**1a**; 0.082 g, 1 mmol). The reaction mixture was stirred at 20–25 °C for 24 h. Column chromatography afforded propanenitrile **5a** (0.171 g, 54%) as a faintly colored powder, mp 170–172 °C (diastereomers ratio being 10:2.0). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.08–7.39 (m, 10H, 11–15, 17–21-H), 6.81 (s, 1H, 4-H), 6.73 (s, 1H, 5-H), 5.63 (d, 1H, 7-H), 4.91 (d, 1H, 6-H, $^3J_{6\text{-H},7\text{-H}}$=10.8 Hz), 3.45 (s, 3H, *N*–*CH*$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.3 (C-8), 145.5 (C-2), 136.2 (C-10), 134.4 (C-16), 134.0 (C-19), 128.8 (C-17, 21), 128.7 (C-12, 14), 128.6 (C-18, 20), 128.3 (C-11, 15), 128.1 (C-13), 126.7 (C-4), 121.2 (C-5), 115.6 (C-9), 43.7 (C-7), 42.2 (C-6), 32.1 (*N*–*CH*$_3$) ppm. ^{15}N NMR (40.55 MHz, $CDCl_3$): δ=−123.7 (CN), −125.6 (N-3), −224.9 (N-1) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.90 (s, 1H,

4-H′), 6.84 (s, 1H, 5-H′), 5.54 (d, 1H, 7-H′), 4.95 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.51 (s, 3H, *N*–C*H*$_3$) ppm. IR (KBr): 2236 (CN), 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.49; H, 5.68; N, 13.76.

*4.3.2. (Z)-3-[(1-Methyl-1H-imidazol-2-yl)(phenyl)methoxy]-3-phenyl-2-propenenitrile (**6**).* The fraction representing an 'ether', propenenitrile **6** (0.011 g, 3%) as a yellow oil, was isolated in the course of propanenitrile **5a** synthesis. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.55–7.15 (m, 10H, 12–16, 18–22-H), 6.96 (s, 1H, 4-H), 6.86 (s, 1H, 5-H), 5.80 (s, 1H, 6-H), 5.11 (s, 1H, 9-H), 3.51 (s, 3H, *N*–C*H*$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=168.4 (C-8), 144.9 (C-2), 137.5 (C-11), 136.6 (C-17), 131.0 (C-14), 129.0 (C-13, 15, 19, 21), 128.8 (C-18, 22), 128.4 (C-12, 16), 126.8 (C-4), 121.8 (C-5), 117.2 (C-10, *C*N), 83.4 (C-6), 77.1 (C-9), 33.3 (*N*–*C*H$_3$) ppm. IR (film): 2217 (CN), 1076 (C–O–C) cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.54; H, 5.14; N, 13.10.

*4.3.3. 2-Benzoyl-3-(1-ethyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5b**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-ethylimidazole (**1b**; 0.096 g, 1 mmol) (48 h) gave propanenitrile **5b** (0.167 g, 51%) as a faintly colored powder, mp 160–162 °C (diastereomers ratio being 10:1.8). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.06–7.40 (m, 10H, 11–15, 17–21-H), 6.79 (s, 1H, 4-H), 6.75 (s, 1H, 5-H), 5.67 (d, 1H, 7-H), 4.88 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 3.45 (m, 2H, C*H*$_2$ from *N*–Et), 1.15 (t, 3H, C*H*$_3$ from *N*–Et) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.8 (C-8), 145.2 (C-2), 136.9 (C-10), 134.7 (C-16), 134.4 (C-19), 129.2 (C-17, 21), 129.1 (C-12, 14), 129.0 (C-18, 20), 128.7 (C-11, 15), 128.4 (C-13), 127.0 (C-4), 119.4 (C-5), 116.1 (C-9), 44.2 (C-7), 42.7 (C-6), 40.6 (*C*H$_2$ from *N*–Et), 15.6 (*C*H$_3$ from *N*–Et) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.91 (s, 1H, 4-H′), 6.86 (s, 1H, 5-H′), 5.52 (d, 1H, 7-H′), 4.93 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.93 (m, 2H, C*H*$_2$ from *N*–Et), 1.24 (t, 3H, C*H*$_3$ from *N*–Et) ppm. IR (KBr): 2235 (CN), 1701 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.24; H, 6.02; N, 13.03.

*4.3.4. 2-Benzoyl-3-(1-i-butyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5c**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-*i*-butylimidazole (**1c**; 0.124 g, 1 mmol) (90 h) gave propanenitrile **5c** (0.173 g, 48%) as a faintly colored powder, mp 152–154 °C (diastereomers ratio being 10:1.8). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.04–7.35 (m, 10H, 11–15, 17–21-H), 6.79 (s, 1H, 4-H), 6.71 (s, 1H, 5-H), 5.66 (d, 1H, 7-H), 4.85 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 3.48 (m, 2H, C*H*$_2$ from *N*–*i*-Bu), 1.87 (m, 1H, *CH* from *N*–*i*-Bu), 0.87–0.72 (m, 6H, 2C*H*$_3$ from *N*–*i*-Bu) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.8 (C-8), 145.6 (C-2), 137.1 (C-10), 134.9 (C-16), 134.4 (C-19), 129.2 (C-17, 21), 129.2 (C-12, 14), 129.0 (C-18, 20), 128.8 (C-11, 15), 128.4 (C-13), 127.0 (C-4), 120.9 (C-5), 116.2 (C-9), 53.3 (*C*H$_2$ from *N*–*i*-Bu), 44.4 (C-7), 42.9 (C-6), 29.5 (*C*H from *N*–*i*-Bu), 20.1, 19.9 (2*C*H$_3$ from *N*–*i*-Bu) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.89 (s, 1H, 4-H′), 6.83 (s, 1H, 5-H′), 5.52 (d, 1H, 7-H′), 4.91 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.58 (m, 2H, C*H*$_2$ from *N*–*i*-Bu) ppm. IR (KBr): 2244 (CN), 1698 (C=O) cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 76.80; H, 6.68; N, 11.85.

*4.3.5. 2-Benzoyl-3-(1-n-hexyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5d**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-hexylimidazole (**1d**; 0.152 g, 1 mmol) (144 h) gave propanenitrile **5d** (0.199 g, 52%) as a faintly colored powder, mp 124–126 °C (diastereomers ratio being 10:1.6). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.09–7.39 (m, 10H, 11–15, 17–21-H), 6.83 (s, 1H, 4-H), 6.78 (s, 1H, 5-H), 5.70 (d, 1H, 7-H), 4.90 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 3.74 (m, 2H, C*H*$_2$ from *N*–*n*-Hexyl), 1.62 (m, 2H, C*H*$_2$ from *N*–*n*-Hexyl), 1.45 (m, 2H, C*H*$_2$ from *N*–*n*-Hexyl), 1.21 (m, 4H, 2C*H*$_2$ from *N*–*n*-Hexyl), 0.88 (m, 3H, C*H*$_3$ from *N*–*n*-Hexyl) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.7 (C-8), 145.4 (C-2), 137.1 (C-10), 134.8 (C-16), 134.4 (C-19), 129.2 (C-17, 21), 129.2 (C-12, 14), 129.0 (C-18, 20), 128.7 (C-11, 15), 128.5 (C-13), 127.0 (C-4), 120.1 (C-5), 116.2 (C-9), 45.9 (*C*H$_2$ from *N*–*n*-Hexyl), 44.2 (C-7), 42.8 (C-6), 31.3 (*C*H$_2$ from *N*–*n*-Hexyl), 30.4 (*C*H$_2$ from *N*–*n*-Hexyl), 26.3 (*C*H$_2$ from *N*–*n*-Hexyl), 22.4 (*C*H$_2$ from *N*–*n*-Hexyl), 14.0 (*C*H$_3$ from *N*–*n*-Hexyl) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.95 (s, 1H, 4-H′), 6.89 (s, 1H, 5-H′), 5.57 (d, 1H, 7-H′), 4.96 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.81 (m, 2H, C*H*$_2$ from *N*–*n*-Hexyl) ppm. IR (KBr): 2245 (CN), 1702 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{27}N_3O$: C, 77.89; H, 7.06; N, 10.90. Found: C, 77.63; H, 6.88; N, 10.60.

*4.3.6. 2-Benzoyl-3-[1-(β-n-butylthio)ethyl-1H-imidazol-2-yl]-3-phenylpropanenitrile (**5e**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-(β-*n*-butylthio)ethylimidazole (**1e**; 0.184 g, 1 mmol) (48 h) gave propanenitrile **5e** (0.150 g, 36%) as a faintly colored powder, mp 122–124 °C (diastereomers ratio being 10:1.6). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.15–7.40 (m, 10H, 11–15, 17–21-H), 6.93 (s, 1H, 4-H), 6.92 (s, 1H, 5-H), 5.77 (d, 1H, 7-H), 4.99 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 4.03 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl), 2.69 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl), 2.39 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl), 1.54 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl), 1.44 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl), 0.99 (m, 3H, C*H*$_3$ from *N*-(β-*n*-butylthio)ethyl) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.6 (C-8), 145.3 (C-2), 136.8 (C-10), 134.7 (C-16), 134.5 (C-19), 129.4 (C-17, 21), 129.2 (C-12, 14), 129.0 (C-11, 15, 18, 20), 128.7 (C-13), 127.4 (C-4), 120.6 (C-5), 116.0 (C-9), 46.2 (*C*H$_2$ from *N*-(β-*n*-butylthio)ethyl), 44.2 (C-7), 42.7 (C-6), 32.4 (*C*H$_2$ from *N*-(β-*n*-butylthio)ethyl), 32.2 (*C*H$_2$ from *N*-(β-*n*-butylthio)ethyl), 31.8 (*C*H$_2$ from *N*-(β-*n*-butylthio)ethyl), 22.0 (*C*H$_2$ from *N*-(β-*n*-butylthio)ethyl), 13.7 (*C*H$_3$ from *N*-(β-*n*-butylthio)ethyl) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.05 (s, 1H, 4-H′), 7.03 (s, 1H, 5-H′), 5.60 (d, 1H, 7-H′), 5.08 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 4.13 (m, 2H, C*H*$_2$ from *N*-(β-*n*-butylthio)ethyl) ppm. IR (KBr): 2244 (CN), 1697 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{27}N_3OS$: C, 71.91; H, 6.52; N, 10.06. Found: C, 71.40; H, 6.82; N, 10.40.

*4.3.7. 2-Benzoyl-3-(1-phenyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5f**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-phenylimidazole (**1f**; 0.144 g, 1 mmol) (108 h) gave propanenitrile **5f** (0.194 g, 51%) as a faintly colored powder, mp 156–158 °C (diastereomers ratio being 10:2.3). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.05–7.15 (m, 10H, 11–15, 17–21-H and 5H, H$_{o,\ m,\ p}$ from *N*–Ph), 6.92 (s, 1H, 4-H), 6.89 (s, 1H, 5-H), 5.66 (d, 1H, 7-H), 4.77 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.7 (C-8), 146.3 (C-2), 146.0 (C$_i$ from *N*–Ph), 136.9 (C-10), 134.5 (C-19), 134.4 (C-16), 129.6 (C$_m$ from *N*–Ph), 129.5 (C-17, 21), 129.2 (C-12, 14), 129.1 (C-18, 20), 128.7 (C-11, 15), 128.6 (C$_o$ from *N*–Ph), 128.2 (C-13), 127.8 (C$_p$ from *N*–Ph), 126.6 (C-4), 121.7 (C-5), 116.0 (C-9), 44.3 (C-7), 42.5 (C-6) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.02 (s, 1H, 4-H′), 6.98 (s, 1H, 5-H′), 5.53 (d, 1H, 7-H′), 4.76 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz) ppm. IR (KBr): 2241 (CN), 1700 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{19}N_3O$: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.24; H, 5.39; N, 11.16.

*4.3.8. 2-Benzoyl-3-(1-benzyl-1H-imidazol-2-yl)-3-phenylpropanenitrile (**5g**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), benzaldehyde (**3a**; 0.106 g, 1 mmol), and 1-benzylimidazole (**1g**; 0.158 g, 1 mmol) (72 h, 1 mL THF) gave

propanenitrile **5g** (0.241 g, 62%) as a faintly colored powder, mp 136–138 °C (diastereomers ratio being 10:1.9). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.05–7.37 (m, 10H, 11–15, 17–21-H and 5H, $H_{o,\ m,\ p}$ from *N*–Bn), 6.83 (s, 1H, 4-H), 6.69 (s, 1H, 5-H), 5.65 (d, 1H, 7-H), 4.89 (s, 2H, CH_2 from *N*–Bn), 4.82 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.5 (C-8), 145.9 (C-2), 136.6 (C-10), 135.5 (C_i from *N*–Bn), 134.7 (C-19), 134.3 (C-16), 129.1 (C-17, 21), 128.9 (C-12, 14), 128.8 (C-18, 20), 128.6 (C_m from *N*–Bn), 128.3 (C-11, 15), 128.0 (C-13), 127.4 (C_p from *N*–Bn), 127.1 (C-4), 126.7 (C_o from *N*–Bn), 121.1 (C-5), 116.0 (C-9), 49.4 (CH_2 from *N*–Bn), 44.2 (C-7), 42.7 (C-6) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.91 (s, 1H, 4-H′), 6.90 (s, 1H, 5-H′), 5.49 (d, 1H, 7-H′), 4.97 (s, CH_2 from *N*–Bn), 4.82 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz) ppm. IR (KBr): 2235 (CN), 1697 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.50; H, 5.79; N, 10.48.

*4.3.9. 4-[2-Cyano-1-(1-ethyl-1H-imidazol-2-yl)-3-oxo-3-phenylpropyl]benzenecarbonitrile (**5h**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), 4-cyanobenzaldehyde (**3b**; 0.131 g, 1 mmol), and 1-ethylimidazole (**1b**; 0.096 g, 1 mmol) (27 h, 0.5 mL MeCN) gave benzenecarbonitrile **5h** (0.155 g, 44%) as a faintly colored powder, mp 186–187 °C (diastereomers ratio being 10:1.7). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.03–7.49 (m, 9H, 11, 12, 14, 15, 17–21-H), 6.83 (s, 1H, 4-H), 6.79 (s, 1H, 5-H), 5.69 (d, 1H, 7-H), 4.95 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 3.78 (m, 2H, CH_2 from *N*–Et), 1.21 (t, 3H, CH_3 from *N*–Et) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.0 (C-8), 143.9 (C-2), 142.2 (C-10), 134.7 (C-19), 134.3 (C-16), 132.9 (C-12, 14), 129.6 (C-11, 15), 129.2 (C-18, 20), 129.0 (C-17, 21), 127.7 (C-4), 119.8 (C-5), 118.3 (C-13), 115.7 (C-9), 112.6 (*C*N from 4-CN–Ph), 43.8 (C-7), 42.3 (C-6), 40.7 (CH_2 from *N*–Et), 15.8 (CH_3 from *N*–Et) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.96 (s, 1H, 4-H′), 6.89 (s, 1H, 5-H′), 5.53 (d, 1H, 7-H′), 5.01 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.94 (m, 2H, CH_2 from *N*–Et), 1.31 (t, 3H, CH_3 from *N*–Et) ppm. IR (KBr): 2243 (CN), 1692 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_4O$: C, 74.56; H, 5.12; N, 15.81. Found: C, 74.20; H, 5.63; N, 15.82.

*4.3.10. 2-Benzoyl-3-(1-methyl-1H-imidazol-2-yl)-3-(pyridin-3-yl) propanenitrile (**5i**).* Analogously, the reaction of cyanoacetylene **2a** (0.127 g, 1 mmol), pyridine-3-aldehyde (**3c**; 0.107 g, 1 mmol), and 1-methylimidazole (**1a**; 0.082 g, 1 mmol) (72 h) gave propanenitrile **5i** (0.054 g, 17%) as a faintly colored powder, mp 166–188 °C (diastereomers ratio being 10:2.5). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=8.67–7.35 (m, 9H, 11, 13–15, 17–21-H), 6.80 (s, 1H, 4-H), 6.74 (s, 1H, 5-H), 5.70 (d, 1H, 7-H), 4.96 (d, 1H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.8 Hz), 3.48 (s, 3H from *N*–CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=189.0 (C-8), 149.8 (C-11, 13), 144.7 (C-2), 136.3 (C-15), 134.7 (C-19), 134.2 (C-16), 132.4 (C-10), 129.0 (C-17, 21, 18, 20), 127.2 (C-4), 124.0 (C-14), 121.8 (C-5), 115.6 (C-9), 43.8 (C-7), 39.8 (C-6), 32.5 (*N*–CH_3) ppm. Signals distinguishable for minor stereoisomer: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=6.88 (s, 1H, 4-H′), 6.84 (s, 1H, 5-H′), 5.55 (d, 1H, 7-H′), 5.07 (d, 1H, 6-H′, $^3J_{6\text{-H}',\ 7\text{-H}'}$=10.4 Hz), 3.54 (s, 3H, *N*–CH_3) ppm. IR (KBr): 2243 (CN), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.14; H, 5.10; N, 17.71. Found: C, 72.57; H, 5.35; N, 17.24.

*4.3.11. 4-(1-Butoxyethoxy)-4-methyl-2-[(1-methyl-1H-imidazol-2-yl)(phenyl)methyl]-3-oxopentanenitrile (**5j**).* Analogously, the reaction of 4-(1-butoxyethoxy)-4-methyl-2-pentynenitrile (**2b**; 0.105 g, 0.5 mmol), benzaldehyde (**3a**; 0.053 g, 0.5 mmol), and 1-methylimidazole (**1a**; 0.041 g, 0.5 mmol) (6 h) gave propanenitrile **5j** (0.129 g, 32%) as a yellow oil. Signals distinguishable stereoisomers: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.05, 7.02, 6.84, 6.82 (s, 4H, 4-H), 6.76, 6.75, 6.69 (s, 4H, 5-H), 5.43, 5.29, 5.24, 5.04 (d, 4H, 7-H), 5.18, 5.05, 4.83, 4.69 (q, 4H, 17-H, $^3J_{17\text{-H},\ CH3}$=5.2 Hz), 4.77, 4.75, 4.60, 4.59 (d, 4H, 6-H, $^3J_{6\text{-H},\ 7\text{-H}}$=10.4 Hz), 3.53, 3.50, 3.48, 3.29 (t, 8H, O–18-CH_2–, $^3J_{H,\ H}$=6.4 Hz), 3.43, 3.42, 3.38, 3.36 (s, 12H, *N*–CH_3), 1.60–1.30 (m, 40H, C–16-(CH_3)$_2$, 19, 20-CH_2–), 0.95–0.85 (m, 24H, HC–17-CH_3, 21-CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=204.7, 204.6, 203.5, 203.1 (C-8), 146.0, 145.9, 145.5, 145.3 (C-2), 136.9, 136.8, 136.6, 136.5 (C-10), 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0 (C-11–15), 126.8, 126.7, 126.6 (C-4), 121.4, 121.3, 121.2 (C-5), 116.7, 116.6, 115.8, 115.7 (C-9), 95.7, 95.1, 95.0, 94.5 (C-17), 82.8, 82.7, 81.9, 81.6 (C-16), 63.5, 63.4, 62.7, 62.1 (O–CH_2-18), 43.6, 43.3, 43.0, 42.9 (C-7), 42.7, 42.4, 41.9, 41.8 (C-6), 32.5, 32.4, 31.9, 31.6 (*N*–CH_3), 26.2, 25.3, 24.1, 23.7, 23.6, 23.2, 23.0, 22.0, 20.8, 20.7, 20.5, 20.4, 19.4, 19.4 (CH–17-CH_3, C-16-(CH_3)$_2$, CH_2-19, CH_2-20), 13.9 (CH_3-21) ppm. IR (film): 2243 (CN), 1704 (C=O) cm^{-1}. Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.90; H, 8.05; N, 10.24.

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