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Synthesis of optically active polyheterocycles containing pyrrolidine, imidazole, and 1,2,3-triazole rings ☆

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ABSTRACT

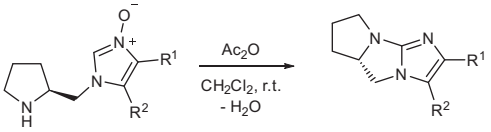
Optically active polyheterocycles containing pyrrolidine, imidazole, and 1,2,3-triazole units were obtained via a multistep synthesis with the [3+2] cycloaddition of Boc-protected (*S*)-(pyrrolidin-2-yl) methyl azide with 2-ethynylimidazoles in the presence of CuI (CuAAC reaction) as the key step. Typical for terminal alkynes, the reactions occurred regioselectively and 1,4-disubstituted 1,2,3-triazoles were formed exclusively. The deprotection of the pyrrolidine N-atom was performed by treatment with TFA under standard conditions.

1. Introduction

Optically active bisheterocycles containing a chiral pyrrolidine skeleton and an imidazole ring can conveniently be prepared from N-protected (*S*)-prolinamine, formaldehyde, and the corresponding α-hydroxyimino ketones.[2] The initially obtained imidazole *N*-oxides of type **1** can be transformed into other imidazole derivatives via deoxygenation, rearrangement, sulfur transfer, and O-alkylation. Recently, the unexpected formation of polyheterocycles **2** via heterocyclization of bisheterocycles **1**, containing the N-deprotected pyrrolidine upon treatment with Ac_2O was reported (Scheme 1).[3]

On the other hand, 2-unsubstituted imidazoles are known to undergo ethynylation by treatment of the corresponding 2-iodo derivative with a silylated acetylene in the presence of $Pd(PPh_3)_4$, CuI, and an organic base (Sonogashira-type alkynylation).[4] The obtained 2-ethynylimidazoles were used for the reaction with different azides to yield 1,2,3-triazole-functionalized imidazoles as biologically active compounds.

In the search for optically active polyheterocycles derived from (*S*)-proline, a series of 2-unsubstituted imidazole *N*-oxides of type **1** were used as substrates for their conversion into optically active polyheterocycles containing a 1,2,3-triazole residue along with imidazole and proline units.



1 2

Scheme 1.

2. Results and discussion

The 2-unsubstituted imidazole *N*-oxides **3** were prepared according to the literature,[5] and subsequently deoxygenated using Raney-Ni in methanolic solution at room temperature.[6] The imidazoles **4** obtained were treated with LDA in THF at −78 °C and iodinated to yield the desired 2-iodo derivatives **5**[4] in good to excellent yields (Scheme 2).

The next step was the reaction of **5** with (trimethylsilyl)acetylene in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in triethylamine as the solvent at 50 °C. The obtained products were desilylated using tetrabutylammonium fluoride (TBAF). After chromatographic purification, the 2-ethynylimidazoles **6** were isolated and characterized by spectroscopic methods (Scheme 3). The most characteristic change in the ^1H NMR spectra in comparison with imidazoles **4** was the signal for the acetylenic CH between 3.23 and 3.58 ppm.

In the final step, azide **7** derived from the Boc-protected (*S*)-proline was reacted with imidazoles **6** following a 'click' procedure.

☆ See Ref. 1.

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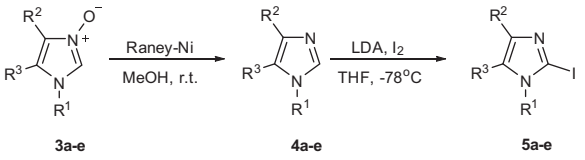


a: $R^1 = R^2 = R^3 = Me$
b: $R^1 = R^2 = Me$, $R^3 = Ph$
c: $R^1 = Me$, $R^2 = R^3 = Ph$
d: $R^1 = Bu$, $R^2 = R^3 = Me$
e: $R^1 = Bu$, $R^2 = Me$, $R^3 = Ph$

Scheme 2.

However, these reactions, performed in acetonitrile solution at 40 °C, required 2 h for complete conversion. The deprotection of the pyrrolidine ring was carried out in a typical manner using TFA in dichloromethane solution. In analogy to the Cu(I)-catalyzed cycloadditions of organic azides to non-symmetric acetylenic dipolarophiles, the reactions leading to **8** occurred with complete regioselectivity. Based on the generally known course of these Cu-catalyzed [3+2] cycloadditions with terminal acetylenes,[7] the structure of the sterically less crowded isomers of type **8** was attributed to all the products obtained. The regioselectivity of the studied azide–alkyne [3+2]-cycloaddition reactions was unambiguously confirmed by 2D NMR methods. For example, in the case of **8c**, the HMBC spectrum showed the correlation of atoms C(5)*H* of the 1,2,3-triazole ring and *C*H_2 of the N(1)CH_2 bridge. Moreover, a correlation of the two protons of the N(1)*C*H_2 group with the C(5) atom of the 1,2,3-triazole unit was also found.

The optically active azide **7** is an attractive building block for the synthesis of optically active 1,2,3-triazoles via the [3+2] cycloaddition with differently substituted acetylenes. Diverse protocols are known for this reaction. Although a classical, non-catalyzed reaction was also reported recently,[8] in general, the cycloaddition was efficiently catalyzed by metal catalysts, such as Cu(I) salts[8a,9,10] and Ru(I) or Ir(I) complexes.[11] Depending on the reaction conditions, the formation of the sterically less crowded 1,2,3-triazole derivatives occurs with either complete regioselectivity or a mixture of the regioisomers is formed.[8a,11] Typically, bisheterocycles containing a pyrrolidine and a less crowded 1,4-disubstituted 1,2,3-triazole ring are reported as products obtained with terminal acetylenes. Trisheterocyclic systems were prepared from **7** and 2-ethynylpyridine[12] and 1-methyl-3-propargylimidazolium chloride,[13], respectively. Using analogous methods, tetra- and pentaheterocyclic compounds with one or two 1,2,3-triazole rings were also synthesized.[12,14]

3. Conclusions

Herein we have reported that azide **7** derived from (*S*)-proline can be efficiently used for the preparation of optically active 1,4-disubstituted 1,2,3-triazole derivatives of type **8** containing three different N-heterocycles. To the best of our knowledge, polyheterocycles of this type are hitherto unknown. They contain three different important heterocyclic units and, therefore, can be considered as attractive model compounds for diverse applications. For example, imidazolyl triazoles have been shown to act as inhibitors of biological processes.[4] In addition, they may also find applications as proline-derived ligands for asymmetric synthesis and organocatalysts.

4. Experimental

4.1. General

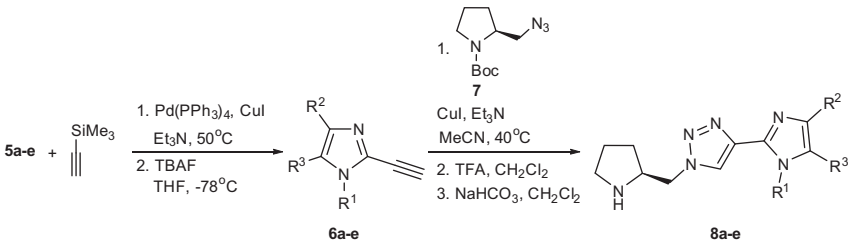
Melting points were determined in a capillary using a Melt-Temp. II apparatus (Aldrich) or STUART SMP30 and are uncorrected. The IR spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions in cm^{-1}. The ^1H and $^{13}C\{1H\}$ NMR spectra were measured on a Bruker Avance III instrument (600 and 150 MHz, resp.) using a solvent signal as the reference. The multiplicity of signals in the ^{13}C NMR spectra was established using the HMQC technique. Chemical shifts (δ) are given in ppm and coupling constants *J* in Hz. The assignments of signals in the ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker maxis spectrometer; ESI-MS: Varian 500. Optical rotations were determined on a PERKIN–ELMER 241 MC polarimeter for $\lambda = 589$ nm.

4.2. General procedure for the synthesis of compounds 3

To a solution of the corresponding *N*-methylidene amine (3.0 mmol) in EtOH (4 mL), a solution of an equimolar amount of the corresponding α-hydroxyimino ketone was added and the reaction mixture was heated at reflux for 3 h. Next, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography or by crystallization. The synthesis of compounds **3a**,[5] **3c**,[5] and **3d**[6] was already described in the literature.

4.2.1. 1,4-Dimethyl-5-phenyl-1*H*-imidazole 3-oxide 3b

Yield: 0.374 g (66%). Colorless crystals. Mp 128–130 °C (Et_2O). IR (KBr): *ν* 3409br, 3147m, 1636m, 1596m, 1501m, 1443m, 1389m, 1338m, 1164m, 1012m, 857m, 769m, 705m, 645m. ^1H NMR ($CDCl_3$): δ 8.06 (s, 1H, HC(2)); 7.52–7.44 (m, 3H, HC(arom.)); 7.34–7.26 (m, 2H, HC(arom.)); 3.55 (s, 3H, Me); 2.22 (s, 3H, Me).



a: $R^1 = R^2 = R^3 = Me$
b: $R^1 = R^2 = Me$; $R^3 = Ph$
c: $R^1 = Me$; $R^2 = R^3 = Ph$
d: $R^1 = Bu$; $R^2 = R^3 = Me$
e: $R^1 = Bu$; $R^2 = Me$; $R^3 = Ph$

Scheme 3.

^{13}C NMR ($CDCl_3$): δ 130.0 (2CH(arom.)); 129.2 (1CH(arom.)); 129.0 (2CH(arom.)); 127.9 (C(5)); 127.3 (C(arom.)); 126.7 (C(4)); 125.9 (C(2)); 33.1 (Me); 7.8 (Me). HR-ESI-MS (MeOH): 189.10224 (calcd 189.10288 for $C_{11}H_{13}N_2O$, $[M+1]^+$).

4.2.2. 1-Butyl-4-methyl-5-phenyl-1*H*-imidazole 3-oxide 3e

Yield: 0.247 g (71%). Colorless crystals. Mp 82–84 °C (Et_2O). IR (KBr): ν 3385br, 3079m, 2963m, 1630m, 1595m, 1464m, 1383m, 1339m, 1165m, 1014m, 768m, 706m, 641m. ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, HC(2)); 7.52–7.45 (m, 3H, HC(arom.); 7.31–7.26 (m, 2H, HC(arom.); 3.83–3.77 (m, 2H, H_2C); 2.20 (s, 3H, Me); 1.60–1.52 (m, 2H, H_2C); 1.25–1.16 (m, 2H, H_2C); 0.83–0.77 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 130.1 (2CH(arom.)); 129.3 (1CH(arom.)); 129.0 (2CH(arom.)); 127.9 (C(5)); 127.6 (C(arom.)); 126.4 (C(4)); 124.8 (C(2)); 45.8 (CH_2); 32.5 (CH_2); 19.3 (CH_2); 13.2 (Me); 7.7 (Me). HR-ESI-MS (MeOH): 231.14919 (calcd 231.14984 for $C_{14}H_{19}N_2O$, $[M+1]^+$).

4.3. General procedure for the synthesis of compounds 4

To a solution of the corresponding imidazole *N*-oxide **3** (1 mmol) in MeOH (3 mL), a suspension of freshly prepared Raney nickel in MeOH was added and the mixture stirred magnetically at room temperature. After all the substrate was consumed (monitored by TLC), the reaction mixture was filtered via Celite and the solvent of the filtrate was evaporated. The obtained imidazoles **4** were purified by column chromatography. The synthesis of compound **4d**[6] was already described in the literature.

4.3.1. 1,4,5-Trimethyl-1*H*-imidazole 4a[15]

Yield: 0.075 g (68%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3393br, 2921m, 1648m, 1597m, 1509m, 1450m, 1423m, 1390m, 1297m, 1233m, 1185m, 1086m, 970m, 752m. ^{1}H NMR ($CDCl_3$): δ 7.01 (s, 1H, HC(2)); 3.23 (s, 3H, MeN); 1.91 (s, 3H, Me); 1.86 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 135.0 (C(2)); 133.2 (C(5)); 122.4 (C(4)); 31.1 (MeN); 12.5 (Me); 7.9 (Me). HR-ESI-MS (MeOH): 111.09167 (calcd 111.09361 for $C_6H_{11}N_2$, $[M+1]^+$).

4.3.2. 1,4-Dimethyl-5-phenyl-1*H*-imidazole 4b[16]

Yield: 0.107 g (62%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3382br, 2951m, 1605m, 1579m, 1500m, 1441m, 1302m, 1260m, 1208m, 1080m, 1015m, 968m, 785m. ^{1}H NMR ($CDCl_3$): δ 7.46–7.40 (m, 2H, HC(arom.)); 7.45 (s, 1H, HC(2)); 7.38–7.34 (m, 1H, HC(arom.)); 7.31–7.27 (m, 2H, HC(arom.)); 3.51 (s, 3H, Me); 2.22 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.8 (C(2)); 135.7 (C(arom.)); 130.3 (C(5)); 129.8 (2CH(arom.)); 128.7 (C(4)); 128.6 (2CH(arom.)); 127.7 (1CH(arom.)); 32.4 (Me); 13.4 (Me). HR-ESI-MS (MeOH): 173.10732 (calcd 173.10935 for $C_{11}H_{13}N_2$, $[M+1]^+$).

4.3.3. 1-Methyl-4,5-diphenyl-1*H*-imidazole 4c[15,17]

Yield: 0.193 g (82%). Colorless crystals. Mp 158–160 °C (CH_2Cl_2/hexane). IR (KBr): ν 3432br, 3042m, 1638m, 1601m, 1507m, 1484m, 1444m, 1423m, 1367m, 1316m, 1250m, 1195m, 1068m, 1021m, 953m, 917m, 772m. ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H, HC(2)); 7.51–7.47 (m, 2H, HC(arom.)); 7.45–7.40 (m, 3H, HC(arom.)); 7.34–7.31 (m, 2H, HC(arom.)); 7.21–7.17 (m, 2H, HC(arom.)); 7.14–7.10 (m, 1H, HC(arom.)); 3.45 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 138.3 (C(arom.)); 137.5 (C(2)); 134.7 (C(arom.)); 130.7 (2CH(arom.)); 130.7 (C(5)); 129.0 (2CH(arom.)); 128.9 (C(4)); 128.6, 128.1, 126.6, 126.3 (6CH(arom.)); 32.5 (Me). HR-ESI-MS (MeOH): 235.12297 (calcd 235.12457 for $C_{16}H_{15}N_2$, $[M+1]^+$).

4.3.4. 1-Butyl-4-methyl-5-phenyl-1*H*-imidazole 4e

Yield: 0.177 g (83%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3381br, 2958m, 1606m, 1493m, 1442m, 1380m, 1262m, 1205m, 1114m, 1015m, 968m, 918m, 702m. ^{1}H NMR ($CDCl_3$): δ 7.36 (s, 1H, HC(2)); 7.34–7.29 (m, 2H, HC(arom.)); 7.26–7.22 (m, 1H, HC(arom.)); 7.19–7.15 (m, 2H, HC(arom.)); 3.74–3.69 (m, 2H, H_2C); 2.09 (s, 3H, Me); 1.44–1.37 (m, 2H, H_2C); 1.10–1.04 (m, 2H, H_2C); 0.71–0.66 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 135.9 (C(2)); 135.3 (C(arom.)); 130.5 (C(5)); 129.9, 128.5 (4CH(arom.)); 128.1 (C(4)); 127.7 (CH(arom.)); 45.0 (CH_2); 32.7 (CH_2); 19.5 (CH_2); 13.3 (Me); 13.1 (Me). HR-ESI-MS (MeOH): 215.15427 (calcd 215.15679 for $C_{14}H_{19}N_2$, $[M+1]^+$).

4.4. General procedure for the synthesis of compounds 5

To a solution of the corresponding imidazole **4** (1 mmol) in dry THF (4 mL), a solution of 1.5 equiv of LDA in THF was added at −78 °C. After 1 h, a solution of I_2 in dry THF was added dropwise and the mixture was stirred overnight at room temperature. Next, $NH_4Cl_{(aq)}$ was added and the mixture extracted with AcOEt. The organic layers were combined and dried over Na_2SO_4. After filtration, the solvent of the filtrate was evaporated under reduced pressure. The crude products were filtered through a short SiO_2 column.

4.4.1. 2-Iodo-1,4,5-trimethyl-1*H*-imidazole 5a

Yield: 0.158 g (67%). Pale yellow crystals. Mp 180–182 °C (MeOH/hexane). IR (KBr): ν 3432br, 2918m, 1610m, 1458m, 1438m, 1395m, 1384m, 1274m, 1195m, 1116m, 1086m, 975m, 762m, 718m. ^{1}H NMR ($CDCl_3$): δ 3.46 (s, 3H, Me); 2.19 (s, 3H, Me); 2.15 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 137.1, 127.0 (C(5), C(4)); 87.4 (C–I); 34.2 (Me); 12.8 (Me); 9.7 (Me). HR-ESI-MS (MeOH): 236.98832 (calcd 236.99005 for $C_6H_{10}N_2I$, $[M+1]^+$).

4.4.2. 2-Iodo-1,4-dimethyl-5-phenyl-1*H*-imidazole 5b

Yield: 0.293 g (98%). Pale yellow crystals. Mp 110–112 °C (MeOH/hexane). IR (KBr): ν 3422br, 2922m, 1636m, 1493m, 1451m, 1386m, 1282m, 1244m, 1095m, 1014m, 920m, 795m, 753m, 700m. ^{1}H NMR ($CDCl_3$): δ 7.49–7.45 (m, 2H, HC(arom.)); 7.43–7.39 (m, 1H, HC(arom.)); 7.31–7.26 (m, 2H, HC(arom.)); 3.50 (s, 3H, Me); 2.23 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 137.1 (C(arom.)); 133.0 (C(5)); 130.2, 128.8, 128.7 (5CH(arom.)); 125.6 (C(4)); 92.4 (C–I); 35.7 (Me); 12.8 (Me). HR-ESI-MS (MeOH): 299.00397 (calcd 299.00539 for $C_{11}H_{12}N_2I$, $[M+1]^+$).

4.4.3. 2-Iodo-1-methyl-4,5-diphenyl-1*H*-imidazole 5c

Yield: 0.231 g (64%). Pale yellow crystals. Mp 160–162 °C (MeOH/hexane). IR (KBr): ν 3433br, 3066m, 1600m, 1504m, 1452m, 1401m, 1360m, 1296m, 1092m, 1071m, 975m, 915m, 770m, 693m, 602m. ^{1}H NMR ($CDCl_3$): δ 7.46–7.40 (m, 5H, HC(arom.)); 7.30–7.27 (m, 2H, HC(arom.)); 7.18–7.14 (m, 2H, HC(arom.)); 7.13–7.09 (m, 1H, HC(arom.)); 3.39 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 141.6, 133.9 (2C(arom.)); 132.7, 130.8 (C(5), C(4)); 130.8, 129.1, 129.1, 128.1, 126.7, 126.6 (10CH(arom.)); 91.6 (C–I); 35.2 (Me). HR-ESI-MS (MeOH): 361.01962 (calcd 361.02049 for $C_{16}H_{14}N_2I$, $[M+1]^+$).

4.4.4. 1-Butyl-2-iodo-4,5-dimethyl-1*H*-imidazole 5d

Yield: 0.153 g (55%). Pale yellow crystals. Mp 38–40 °C (MeOH/hexane). IR (KBr): ν 3373br, 2958m, 1597m, 1467m, 1417m, 1370m, 1308m, 1210m, 1120m, 1010m, 980m, 765m. ^{1}H NMR ($CDCl_3$): δ 3.80–3.76 (m, 2H, H_2C); 2.20 (s, 3H, Me); 2.15 (s, 3H, Me); 1.66–1.59 (m, 2H, H_2C); 1.42–1.34 (m, 2H, H_2C); 0.99–0.95 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.9, 126.4 (C(5), C(4)); 87.3 (C–I); 47.4 (CH_2); 32.4 (CH_2); 19.9 (CH_2); 13.7 (Me); 12.7 (Me); 9.5 (Me). HR-ESI-MS (MeOH): 279.03527 (calcd 279.03650 for $C_9H_{16}N_2I$, $[M+1]^+$).

4.4.5. 1-Butyl-2-iodo-4-methyl-5-phenyl-1*H*-imidazole 5e

Yield: 0.333 g (98%). Pale yellow crystals. Mp 56–58 °C (MeOH/hexane). IR (KBr): ν 3057br, 2958m, 1606m, 1582m, 1493m,

1459m, 1410m, 1274m, 1016m, 911m, 785m, 756m, 701m. ^{1}H NMR ($CDCl_3$): δ 7.50–7.42 (m, 3H, HC(arom.)), 7.32–7.29 (m, 2H, HC(arom.)), 3.79–3.74 (m, 2H, H_2C); 2.19 (s, 3H, H_3C); 2.14 (s, 3H, H_3C); 1.65–1.58 (m, 2H, H_2C); 1.42–1.34 (m, 2H, H_2C); 0.99–0.94 (m, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 137.2, 132.8 (C(5), C(4)); 130.3 (2HC(arom.)); 129.2 (C(arom.)); 129.9, 128.9 (3HC(arom.)); 90.4 (C–I); 47.8 (CH_2); 32.4 (CH_2); 19.6 (CH_2); 13.4 (Me); 12.6 (Me). HR-ESI-MS (MeOH): 341.05092 (calcd 341.05239 for $C_{14}H_{18}N_2I$, $[M+1]^+$).

4.5. General procedure for the synthesis of compounds 6

To a solution of the corresponding iodoimidazole **5** (1 mmol), Pd(PPh_3)$_4$ (0.2 mmol), and CuI (0.4 mmol) in dry Et_3N (5 mL), trimethylsilylacetylene (1.2 mmol) was added dropwise. The mixture was heated at 50 °C until the substrate was consumed (ca. 30 min). Next, the precipitate was filtered and washed with Et_2O. The solvent was evaporated and the crude product was purified by column chromatography (Al_2O_3, AcOEt/hexane 1:9). The obtained product was dissolved in dry THF and TBAF (1.5 equiv) was added to the solution at −78 °C. After 20 min, H_2O was added to the mixture, which was then extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4. After filtration, the solvent was evaporated. Product **6** was purified by column chromatography (AcOEt/hexane 3:7).

4.5.1. 2-Ethynyl-1,4,5-trimethyl-1*H*-imidazole 6a

Yield: 0.069 g (52%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (KBr): *v* 3111br, 2984m, 2098m, 1585m, 1466m, 1405m, 1378m, 1162m, 821m, 746m, 729m. ^{1}H NMR ($CDCl_3$): δ 3.48 (s, 3H, Me); 3.23 (s, 1H, HC); 2.07 (s, 3H, Me); 2.05 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 134.5, 128.6, 124.6 (3C(imid.)); 80.6, 73.9 (C≡C); 31.1 (Me); 12.7 (Me); 8.9 (Me). HR-ESI-MS (MeOH): 135.09162 (calcd 135.09167 for $C_8H_{11}N_2$, $[M+1]^+$).

4.5.2. 2-Ethynyl-1,4-dimethyl-5-phenyl-1*H*-imidazole 6b

Yield: 0.094 g (48%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): *v* 3230br, 2918m, 2109m, 1566m, 1487m, 1449m, 1390m, 1018m, 762m, 707m, 655m, 635m. ^{1}H NMR ($CDCl_3$): δ 7.48–7.44 (m, 2H, HC(arom.)); 7.41–7.37 (m, 1H, HC(arom.)); 7.31–7.27 (m, 2H, HC(arom.)); 3.58 (s, 3H, Me); 3.36 (s, 1H, HC); 2.20 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.2, 130.2, 130.0, 129.8 (C(arom.), 3C(imid.)); 129.8, 128.7, 128.2 (5CH(arom.)); 81.3, 73.8 (C≡C); 32.3 (Me); 13.4 (Me). HR-ESI-MS (MeOH): 197.10756 (calcd 197.10732 for $C_{13}H_{13}N_2$, $[M+1]^+$).

4.5.3. 2-Ethynyl-1-methyl-4,5-diphenyl-1*H*-imidazole 6c

Yield: 0.126 g (49%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (KBr): *v* 3299br, 2924m, 2853m, 2118m, 1599m, 1504m, 1478m, 1461m, 1447m, 1387m, 1073m, 964m, 778m, 756m, 697m. ^{1}H NMR ($CDCl_3$): δ 7.53–7.47 (m, 5H, HC(arom.)); 7.38–7.34 (m, 2H, HC(arom.)); 7.24–7.16 (m, 3H, HC(arom.)); 3.57 (s, 3H, Me); 3.44 (s, 1H, HC). ^{13}C NMR ($CDCl_3$): δ 138.6, 133.9, 130.8, 130.3, 130.2 (2C(arom.), 3C(imid.)); 130.6, 129.1, 128.9, 128.1, 126.9, 126.7 (10CH(arom.)); 81.8, 73.6 (C≡C); 32.1 (Me). HR-ESI-MS (MeOH): 259.12283 (calcd 259.12298 for $C_{18}H_{15}N_2$, $[M+1]^+$).

4.5.4. 1-Butyl-2-ethynyl-4,5-dimethyl-1*H*-imidazole 6d

Yield: 0.089 g (51%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): *v* 3428br, 2958m, 2872m, 2112m, 1735m, 1578m, 1467m, 1410m, 1369m, 1214m, 1007m, 830m, 704m. ^{1}H NMR ($CDCl_3$): δ 3.94–3.89 (m, 2H, H_2C); 3.28 (s, H, HC); 2.14 (s, 3H, Me); 2.13 (s, 3H, Me); 1.70–1.64 (m, 2H, H_2C); 1.39–1.32 (m, 2H, H_2C); 0.94 (*t*, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 134.7, 128.4, 123.9 (3C(imid.)); 80.3, 74.2 (C≡C); 44.6 (CH_2); 32.6 (CH_2); 19.8 (CH_2); 13.6 (Me); 12.8 (Me); 8.9 (Me). HR-ESI-MS (MeOH): 177.13848 (calcd 177.13863 for $C_{11}H_{17}N_2$, $[M+1]^+$).

4.5.5. 1-Butyl-2-ethynyl-4-methyl-5-phenyl-1*H*-imidazole 6e

Yield: 0.099 g (42%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): *v* 3336br, 2959m, 2123m, 1489m, 1460m, 1405m, 1377m, 1315m, 761m, 702m, 610m, 596m, 508m, 454m. ^{1}H NMR ($CDCl_3$): δ 7.47–7.43 (m, 2H, HC(arom.)); 7.41–7.38 (m, 1H, HC(arom.)); 7.29–7.26 (m, 2H, HC(arom.)); 3.98–3.94 (m, 2H, H_2C); 3.34 (s, 1H, HC); 2.16 (s, 3H, Me); 1.55–1.49 (m, 2H, H_2C); 1.19–1.12 (m, 2H, H_2C); 0.77 (*t*, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.3, 130.1, 129.7, 129.5 (C(arom.), 3C(imid.)); 129.9, 128.7, 128.2 (5HC(arom.)); 80.9, 74.0 (C≡C); 44.9 (CH_2); 32.5 (CH_2); 19.5 (CH_2); 13.4 (Me); 13.2 (Me). HR-ESI-MS (MeOH): 239.15403 (calcd 239.15428 for $C_{16}H_{19}N_2$, $[M+1]^+$).

4.6. General procedure for the synthesis of compounds 8

To a solution of the corresponding acetylene derivative **6** (1 mmol) and CuI (0.2 mmol) in acetonitrile (3 mL) under an argon atmosphere, Et_3N (3 mL) was added. After 15 min, to the yellow reaction mixture was added dropwise azide **7**[18] (1 mmol) in acetonitrile (2 mL) and heated at 40 °C for 2 h. Next, H_2O was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (3 mL) and trifluoroacetic acid (1.5 equiv) in CH_2Cl_2 (2 mL) was added. After all the intermediate was consumed (monitored by TLC), the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (4 mL). Next, $NaHCO_3$ was added and the mixture was magnetically stirred for 5 h. The solid was then filtered and the filtrate was concentrated by evaporation in a rotary evaporator. The crude product **8** was purified by column chromatography.

4.6.1. 4-(1,4,5-Trimethyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole 8a

Yield: 0.119 g (46%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): *v* 3399br, 2903m, 2824m, 1646m, 1582m, 1459m, 1289m, 1213m, 1013m, 856m, 748m, 618m. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H, HC(triaz.)); 4.46–4.40 (m, 1H, HC); 4.34–4.28 (m, 1H, H_2C); 3.95 (s, 3H, Me); 3.69–3.63 (m, 1H, H_2C); 3.04–2.94 (m, 2H, H_2C); 2.21 (s, 3H, Me); 2.21 (s, 3H, Me); 2.01–1.94 (m, 1H, H_2C); 1.85–1.72 (m, 2H, H_2C); 1.57–1.49 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): δ 141.2, 136.9, 133.2, 124.5 (3C(imid.), C(triaz.)); 123.1 (CH(triaz.)); 57.9 (CH); 55.3 (CH_2); 46.4 (CH_2); 32.1 (Me); 29.1 (CH_2); 25.3 (CH_2); 12.6 (Me); 8.8 (Me). HR-ESI-MS (MeOH): 261.18240 (calcd 261.18222 for $C_{13}H_{21}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = −26 (*c* 0.5, CH_2Cl_2).

4.6.2. 4-(1,4-Dimethyl-5-phenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole 8b

Yield: 0.197 g (61%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): *v* 3420br, 2925m, 2854m, 2468m, 1683m, 1635m, 1480m, 1312m, 1203m, 1177m, 1131m, 1048m, 1017m, 833m, 801m, 721m, 703m. ^{1}H NMR ($CDCl_3$): δ 8.53 (s, 1H, HC(triaz.)); 7.37–7.30 (m, 3H, HC(arom.)); 7.16–7.13 (m, 2H, HC(arom.)); 4.71–4.58 (m, 2H, H_2C); 4.01–3.94 (m, 1H, HC); 3.52 (s, 3H, Me); 3.32–3.25 (m, 1H, H_2C); 3.16–3.09 (m, 1H, H_2C); 2.16 (s, 3H, Me); 2.16–2.08 (m, 1H, H_2C); 2.06–1.97 (m, 1H, H_2C); 1.94–1.85 (m, 1H, H_2C); 1.79–1.69 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): δ 139.8, 138.9, 134.9, 130.6, 130.1, 129.5, 128.8, 128.1 (C(arom.), 3C(imid.), C(triaz.), 5CH(arom.)); 123.2 (CH(triaz.)); 59.9 (CH); 52.9 (CH_2); 45.6 (CH_2); 32.9 (Me); 28.7 (CH_2); 24.1 (CH_2); 12.8 (Me). HR-ESI-MS (MeOH): 323.19803 (calcd 323.19787 for $C_{18}H_{23}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = −19 (*c* 0.625, CH_2Cl_2).

4.6.3. 4-(1-Methyl-4,5-diphenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole 8c

Yield: 0.276 g (65%). Pale yellow crystals. Mp 52–54 °C (MeOH/hexane). IR (film): *ν* 3424br, 2954m, 2854m, 2202m, 2173m, 1683m, 1602m, 1503m, 1443m, 1400m, 1202m, 1133m, 1055m, 722m, 696m, 640m. ^{1}H NMR ($CDCl_3$): *δ* 8.45 (s, 1H, HC(triaz.)); 7.44–7.39 (m, 5H, HC(arom.)); 7.34–7.30 (m, 2H, HC(arom.)); 7.20–7.16 (m, 2H, HC(arom.)); 7.15–7.11 (m, 1H, HC(arom.)); 4.60–4.54 (m, 2H, H_2C); 3.83–3.77 (m, 1H, HC); 3.77 (s, 3H, Me); 3.14–3.08 (m, 1H, H_2C); 3.05–2.99 (m, 1H, H_2C); 2.04–1.96 (m, 1H, H_2C); 1.91–1.84 (m, 1H, H_2C); 1.80–1.71 (m, 1H, H_2C); 1.68–1.60 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): *δ* 140.2, 138.9, 137.9 (3C(imid.)); 134.4, 130.9, 130.8, 130.3, 129.0, 128.7, 128.2, 127.2, 126.7 (2C(arom.), C(triaz.), 10CH(arom.)); 124.3 (CH(triaz.)); 58.7 (CH); 53.5 (CH_2); 46.1 (CH_2); 33.1 (Me); 28.9 (CH_2); 24.7 (CH_2). HR-ESI-MS (MeOH): 385.21378 (calcd 385.21352 for $C_{23}H_{25}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = −29 (*c* 0.5, CH_2Cl_2).

4.6.4. 4-(1-Butyl-4,5-dimethyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole 8d

Yield: 0.117 g (39%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): *ν* 3400br, 2968m, 2854m, 1625m, 1562m, 1477m, 1399m, 1286m, 1050m, 812m, 733m, 599m. ^{1}H NMR ($CDCl_3$): *δ* 8.32 (s, 1H, HC(triaz.)); 4.66–4.57 (m, 1H, H_2C); 4.54–4.46 (m, 1H, H_2C); 4.11–3.99 (m, 2H, H_2C); 3.91–3.82 (m, 1H, HC); 3.45–3.36 (m, 1H, H_2C); 3.23–3.12 (m, 1H, H_2C); 3.19–3.00 (m, 1H, H_2C); 2.12 (s, 3H, Me); 2.09 (s, 3H, Me); 2.06–1.98 (m, 1H, H_2C); 1.96–1.88 (m, 1H, H_2C); 1.85–1.77 (m, 1H, H_2C); 1.69–1.60 (m, 1H, H_2C); 1.57–1.37 (m, 3H, H_2C); 0.85 (*t*, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): *δ* 139.7, 136.4, 132.9, 124.0 (3C(imid.), C(triaz.)); 122.9 (CH(triaz.)); 59.1 (CH); 54.4 (CH_2); 53.3 (CH_2); 45.7 (CH_2); 44.6 (CH_2); 32.6 (CH_2); 28.9 (CH_2); 24.4 (CH_2); 13.6 (Me); 12.2 (Me); 8.7 (Me). HR-ESI-MS (MeOH): 303.22922 (calcd 303.22917 for $C_{16}H_{27}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = −32 (*c* 0.5, CH_2Cl_2).

4.6.5. 4-(1-Butyl-4-methyl-5-phenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole 8e

Yield: 0.174 g (48%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): *ν* 3398br, 2953m, 2862m, 1614m, 1538m, 1443m, 1402m, 1279m, 1039m, 829m, 730m, 608m. ^{1}H NMR ($CDCl_3$): *δ* 8.21 (s, 1H, HC(triaz.)); 7.42–7.37 (m, 2H, HC(arom.)); 7.35–7.31 (m, 1H, HC(arom.)); 7.28–7.25 (m, 2H, HC(arom.)); 4.40–4.22 (m, 4H, H_2C); 3.67–3.56 (m, 1H, HC); 2.96–2.84 (m, 2H, H_2C); 2.12 (s, 3H, Me); 1.93–1.86 (m, 1H, H_2C); 1.77–1.66 (m, 2H, H_2C); 1.48–1.40 (m, 3H, H_2C); 1.09–1.01 (m, 2H, H_2C); 0.63 (*t*, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): *δ* 140.9, 135.3, 130.7, 130.1, 125.9 (3C(imid.), C(arom.), C(triaz.)); 130.4 (2HC(arom.)); 128.6, 127.9 (3HC(arom.)); 123.6 (CH(triaz.)); 61.8 (CH); 55.3 (CH_2); 46.5 (CH_2); 44.9 (CH_2); 32.9 (CH_2); 29.2 (CH_2); 25.4 (CH_2); 19.3 (CH_2); 13.4 (Me); 13.1 (Me). HR-ESI-MS (MeOH): 365.24494 (calcd 365.24482 for $C_{21}H_{29}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = −16 (*c* 0.625, CH_2Cl_2).

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