1,2-Disubstituted Hexahydro-1*H*-benzo[*d*]imidazoles: Synthesis, Characterization, and Stability

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Abstract: Starting from commercially available (hetero)aromatic nitriles and (1*R*,2*R*)-cyclohexane-1,2-diamine, nine NH-imidazolines (hexahydro-1*H*-benzo[*d*]imidazoles) were synthesized in good yields. The molecular structures of three imidazolines were confirmed by X-ray analysis. N-Benzylation afforded some of the desired *N*-benzylimidazolines, but was incompatible with imidazolines that possessed strong electron-accepting heteroaromatic groups at C2. In the latter cases, the products decomposed during column chromatography to form N,N′-disubstituted cyclohexane-1,2-diamines.

Key words: heterocycles, imidazolines, chiral pool, N-benzylation, stability

Optically active molecules featuring imidazole or imidazoline (dihydroimidazole) cores constitute an important class of organic compounds. They have been used in a variety of chemistry applications including the following: nitrogen ligands coordinating transition metals,[1,2] biologically active substances (IBS, imidazoline binding site),[3] ionic liquids,[4] and N-heterocyclic carbenes (NHCs).[5,6] Due to the presence of stereogenic centers directly at C4(C5) of the imidazoline ring, imidazolines[7] have also been widely used as chiral auxiliaries resembling oxazolines.[8,9] However, in contrast to oxazolines, imidazolines offer the possibility for N-functionalization to fine-tune their electronic properties.[10] Optically active imidazoline derivatives efficiently catalyze a wide range of asymmetric reactions including allylation, hydrogenation, and addition of diethylzinc to aldehydes, along with Heck reactions and many others.[1,11–13] Currently, imidazolines are perhaps the most often employed ligands and, despite recent progress in their preparation,[14] they are most commonly prepared by condensation of readily available chiral 1,2-diamines with carboxylic acids and their derivatives, such as imidates, amidines, esters, acyl chlorides, and nitriles.

As a part of our research focused on the development of new terpene-derived imidazolines, we have recently reported the synthesis and application of terpene-annulated imidazoles **1**–**3** and camphor-annulated imidazolines **4** (Figure 1).[15,16] The synthesis of imidazolines **4** involved the condensation of *exo*-camphordiamine dihydrochloride[17] with picolinimidate generated in situ from pyridine-2-carbonitrile and sodium methoxide. The resulting camphor-imidazoline was further functionalized at the imidazoline nitrogen N1 to afford **4** as a pair of two separable regioisomers. In an effort to extend this study, we decided to modify the imidazoline ligand by replacing the camphor moiety with cyclohexane. Specifically, we proposed hexahydro-1*H*-benzo[*d*]imidazoles **5**–**11** and **12**,**13** (Figure 1), which feature annulated cyclohexane and imidazoline rings and various pendants at C2. As recently reported by Beller et al.,[18,19] pyridine bis-imidazolines (pybim) similar to **13** have shown promising activities in asymmetric epoxidation of alkenes while their catalytic activity can be further tuned by various N-substitutions. Hence, we report herein our attempts to synthesize imidazolines **5**–**11** and **12**,**13**, their full spectral characterization, and attempted N-modification and resulting stability.

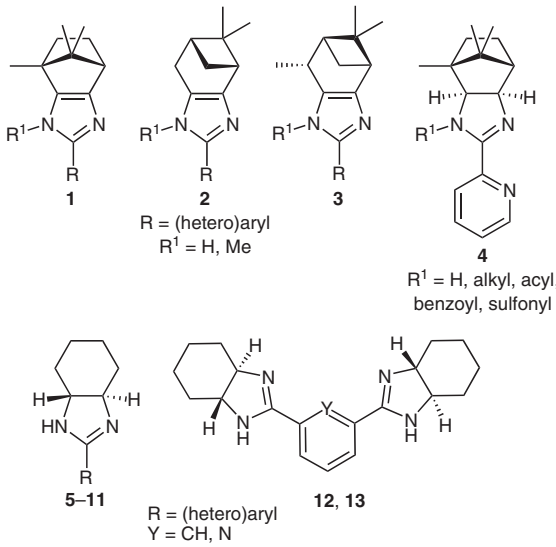

Figure 1 Previous **1**–**4** and newly proposed **5**–**13** imidazoles/imidazolines

The construction of the imidazoline core has been accomplished via a convenient condensation of (hetero)aromatic imidates with (1*R*,2*R*)-cyclohexane-1,2-diamine in a manner similar to that used for the construction of **4**.[16] The

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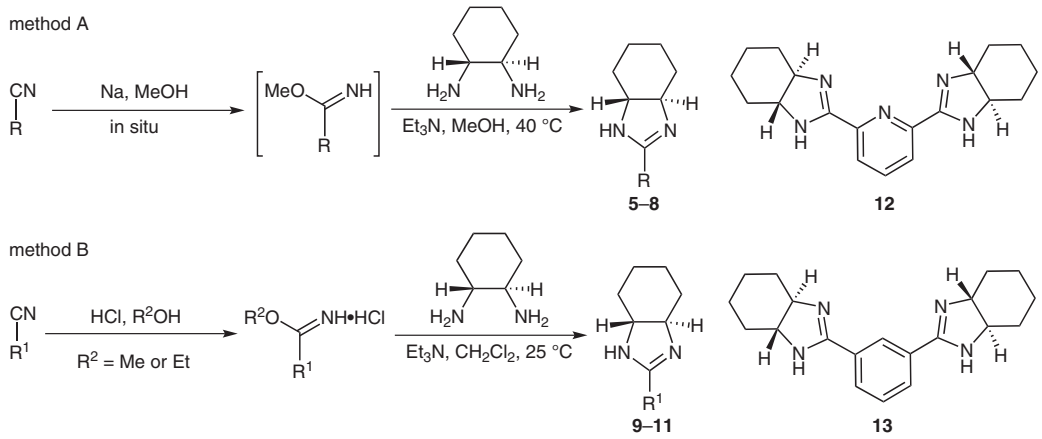


Scheme 1 Synthesis of NH-imidazolines

(hetero)aromatic imidates were synthesized from commercially available nitriles. Whereas the treatment of electron-poor nitriles (R = pyridin-2-yl, pyridine-2,6-diyl, pyrimidin-2-yl, pyrazin-2-yl, and isoquionolin-1-yl) with sodium methoxide in methanol[20] afforded the desired imidates directly within one to three hours [as monitored on TLC (SiO_2, EtOAc) or by GC/MS], electron-rich nitriles (R = phenyl, benzene-1,3-diyl, 1*H*-pyrrol-2-yl, thiophen-2-yl) were treated with gaseous hydrochloric acid in methanol (Pinner synthesis)[21–25] to furnish imidates hydrochlorides. Subsequently, the imidates and imidates hydrochlorides were each condensed with (1*R*,2*R*)-cyclohexane-1,2-diamine in methanol–triethylamine (Method A) or dichloromethane–triethylamine (Method B) to afford the desired NH-imidazolines **5–13** (Scheme 1, Table 1).

Table 1 NH-Imidazolines **5–13** Prepared

Product	R	Method	Yield (%)	Mp (°C)	$[\alpha]_D^{20}$ (*c*)[a]
5	pyridin-2-yl	A	66	110–112	+141.6
6	pyrimidin-2-yl	A	31	157–159	+ 84.4
7	pyrazin-2-yl	A	96	149–152	+159.3
8	isoquinolin-1-yl	A	3[b]	120–122	+ 31.6
9	phenyl	B	94	159–162	+148.0
10	1*H*-pyrrol-2-yl	B	72	309–312	+ 45.0
11	thiophen-2-yl	B	74	199–201	+158.0
12	pyridine-2,6-diyl	A	52	315–322	+192.4
13	benzene-1,3-diyl	B	37	261–263	+215.0

[a] Concentration *c* is 0.5 g/100 mL MeOH.
[b] Problematic synthesis of imidate (see text).

During the sodium methoxide catalyzed conversion of isoquinoline-1-carbonitrile to imidate, facile substitution of the cyano to methoxy group was observed, and as a result, imidazoline **8** was obtained in a low yield. However, all of the prepared NH-imidazolines **5–13** were fully characterized by EI-MS, ^{1}H and ^{13}C NMR, and optical rotations (see Supporting Information). Despite the problematic synthesis of **8**, a slow evaporation of its ethyl acetate solution afforded crystals suitable for X-ray analysis. A similar crystallization procedure for the solution of hydrochloride **12** in chloroform–methanol also afforded measurable crystals. Moreover, a deuterated chloroform solution of **11** with Mosher's acid, used for the determination of optical purity by ^{1}H NMR spectroscopy, crystallized directly in an NMR tube to provide suitable crystals. Thus, we were able to confirm the molecular structures of imidazolines **8**, **11**, and **12** by X-ray crystal structure analysis (Figures 2– 4, see also Supporting Information). The ORTEP plots in Figures 2– 4 show the several key features: the spatial arrangement and solid-state structures of the prepared Mosher salts of **11** (Figure 3), hydrogen bonding of HCl to **12** (Figure 4) and confirmed the absolute configurations of each stereogenic centre.

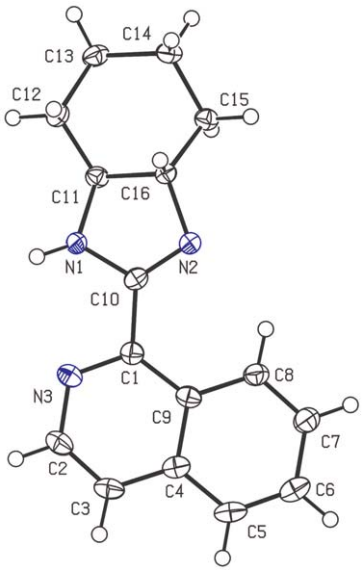


Figure 2 Crystal structure of **8**; vibrational ellipsoids of the ORTEP plot are shown at the 50% probability level (R = 0.06, 150 K)

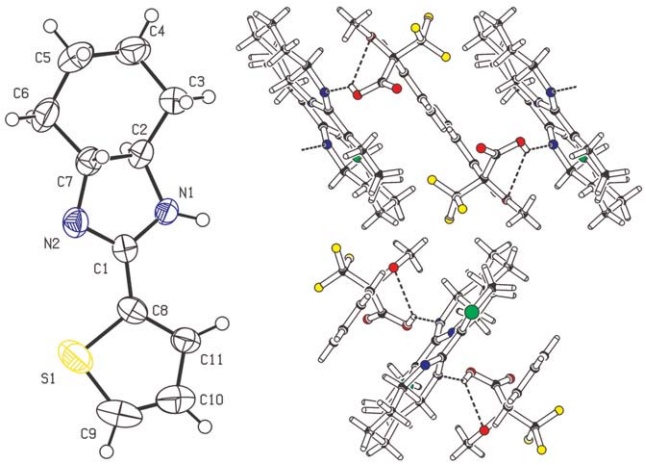


Figure 3 Crystal structure of **11** (left) and crystal packing of the Mosher's salts of **11** (right); vibrational ellipsoids of the ORTEP plot are shown at the 50% probability level (R = 0.07, 150 K), molecules of solvent omitted for clarity

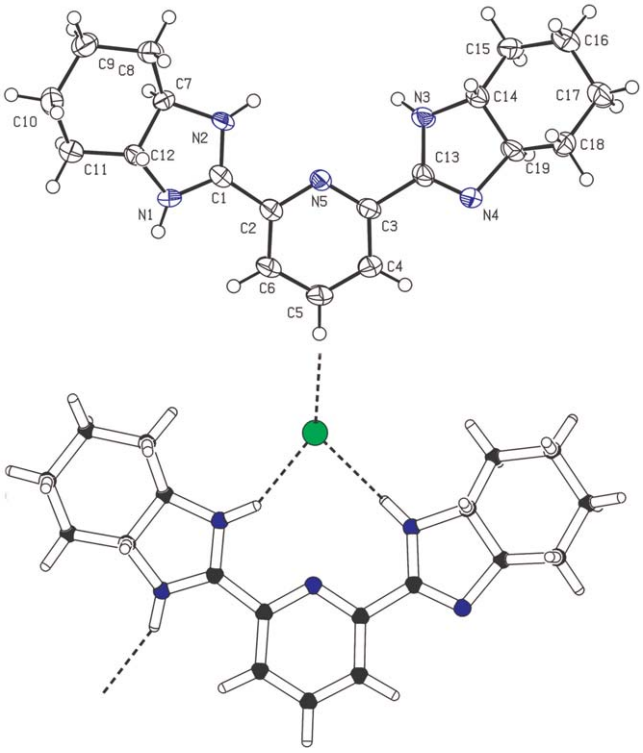
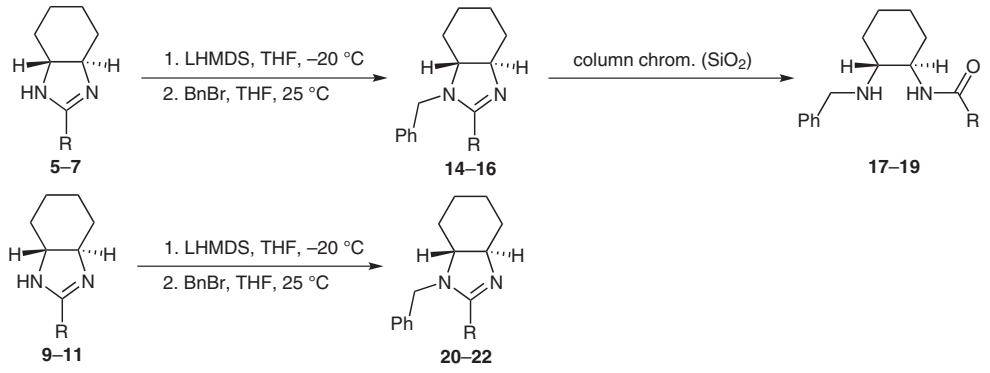


Figure 4 Crystal structure of **12** (up) and its hydrogen bonding to HCl (down); vibrational ellipsoids of the ORTEP plot are shown at the 50% probability level (R = 0.07, 150 K)

In the next reaction step, N-alkylation of the prepared imidazolines was attempted. Treatment of imidazolines **5–7** and **9–11** with 1.3 equivalents lithium bis(trimethylsilyl)amide (LHMDS) and subsequent reaction with benzyl bromide afforded *N*-benzylimidazolines **14–16** and **20–22** (Scheme 2, Table 2).

However, decomposition of the electron-poor imidazolines **14–16** occurred during purification by column chromatography (SiO_2) or within a few days upon standing to yield N,N′-disubstituted (1*R*,2*R*)-cyclohexane-1,2-diamines **17–19** (Scheme 2, Table 2). We have observed such imidazoline ring opening previously only for *N*-sulfonyl camphor-imidazolines **4**.[16] However the decomposition of imidazolines **14–16** proceeded to such a degree that N-alkylation as well as other attempted N-substitutions led to pure N,N′-disubstituted (1*R*,2*R*)-cyclohexane-1,2-diamines **17–19**. Only the imidazolines **15** and **16** with pyrimidin-2-yl and pyrazin-2-yl R substituents could be isolated as pure compounds, although their decomposition to **18** and **19** did occur after two days. Whereas the ring opening in imidazolines **14–16** was facilitated by the presence of electron-accepting substituents at C2 [R = pyridin-2-yl, pyrimidin-2-yl and pyrazin-2-yl], imidazolines **20–22** with substituents such as phenyl, 1*H*-pyrrol-2-yl, and thiophen-2-yl were more stable. However, a slow decomposition occurred after few weeks. Finally, N-alkylation of imidazolines **12** and **13** proved to be unfeasible due to the formation of an inseparable mixture of three to four products. It should be noted that the above-mentioned decomposition occurred independently on the alkylating or acylating agent used.

In this work, we have demonstrated a facile synthesis of optically pure imidazolines annulated with cyclohexane (1,2-disubstituted hexahydro-1*H*-benzo[*d*]imidazoles). Overall nine NH-imidazolines, six of which had not been previously prepared, were synthesized from commercially available precursors. NH-Imidazolines **9**, **11**, and **12** were already synthesized previously by other methods.[19,26,27] The molecular structures of imidazolines **8**, **11**, and **12** were confirmed by X-ray analysis. In certain cases,



Scheme 2 Attempted N-substitution of imidazolines **5–7** and **9–11**

Table 2 *N*-Benzylimidazolines **14**–**16** and **20**–**22**, and 1,2-Diamines **17**–**19** Prepared

Product	R	Yield (%)	$[\alpha]_D^{20}$ (*c*)[a]
14[b]	pyridin-2-yl	–	–
15	pyrimidin-2-yl	31	+ 52.4
16	pyrazin-2-yl	46	+ 75.4
17	pyridin-2-yl	37	– 30.0
18	pyrimidin-2-yl	38	– 19.6
19	pyrazin-2-yl	35	– 31.6
20	phenyl	58	+ 31.2
21	1*H*-pyrrol-2-yl	65	+136.0
22	thiophen-2-yl	59	+ 67.2

[a] Concentration *c* is 0.5 g/100 mL MeOH.
[b] Detected only by GC/MS (see Supporting Information).

N-alkylation of the prepared imidazolines proved to be complicated by the subsequent imidazoline ring opening, which led to N,N′-disubstituted (1*R*,2*R*)-cyclohexane-1,2-diamines. The ring opening occurred by column chromatography (SiO_2) or upon standing. Based on our observations, this decomposition was facilitated by the presence of electron-accepting substituents at C2 of the imidazoline and, consequently, the imidazolines with pyridin-2-yl, pyrimidin-2-yl, and pyrazin-2-yl substituents were isolated in small yields or were not isolated at all. On the other hand, imidazolines bearing phenyl, 1*H*-pyrrol-2-yl and thiophen-2-yl substituents were more stable and could be isolated in 58–65% yields. However, their decomposition was observed upon standing for few weeks. In light of the large number of published imidazolines, it is somewhat curious that there have been no prior reports of their instability and facile ring-opening. However, in 2006 Braddock et al.[28,29] reported on a convenient preparation of enantiomerically pure 1,2-diphenylethane-1,2-diamine (DPEDA) that utilized the synthesis of *N*-acyl-2,4,5-triphenylimidazoline (*N*-acyl-*iso*-amarine) and its subsequent acid-catalyzed ring opening (aq HCl). This reaction afforded N,N′-disubstituted-1,2-diphenylethane-1,2-diamines in a similar way as for **17**–**19**.

Reagents and solvents were reagent-grade and were purchased from Penta, Aldrich, and Acros, and used as received. Column chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. TLC was conducted on aluminum sheets coated with silica gel 60 F_{254} obtained from Merck, with visualization by UV lamp (254 or 360 nm). EtOAc–MeOH–aqNH_3 (1:1:0.01) was used as the solvent system for determining all R_f values. Melting points were measured on a Büchi B-540 melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 360/400/500 MHz and 90/100/125 MHz, respectively, on a Bruker AMX 360 or Bruker Avance 400/500 instrument at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. The residual solvent signal in the ^{1}H and ^{13}C NMR spectra was used as an internal reference ($CDCl_3$: 7.25 and 77.23 ppm; MeOD: 3.31 and 49.15 ppm). Coupling constants (*J*) are given in Hz. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Protons of the substituents at the C2-position are marked as follows: Ph (phenyl), Py (pyridin-2-yl), Pm (pyrimidin-2-yl), Pz (pyrazin-2-yl), Isq (isoquinolin-2-yl), Ph (phenyl), Pyr (1*H*-pyrrol-2-yl), Th (thiophen-2-yl), Py2 (pyridine-2,6-diyl), and Ben (benzene-1,3-diyl). The protons of the benzyl substituent at the N1-position are marked as Bn. Additional NMR techniques such as ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMBC and ^{1}H–^{13}C HMQC were used for regular signal assignment. Some of the cyclohexane carbons were not observed in ^{13}C NMR spectra as a result of imidazoline tautomerism (averaged signals). The mass spectra were measured on a GC/MS configuration comprised of an Agilent Technologies – 6890N gas chromatograph (HP-5MS column, length 30 m, I.D. 0.25 mm, film 0.25 μm) equipped with a 5973 Network MS detector (EI 70 eV, mass range 33–550 Da). Elemental analyses were performed on an EA 1108 Fisons instrument. Optical rotation values were measured on a Perkin-Elmer 341 instrument, concentration *c* is given in g/100 mL MeOH.

For spectral characterization of methyl 1*H*-pyrrole-2-carbimidate hydrochloride, methyl thiophene-2-carbimidate hydrochloride and NH-imidazolines **9**, **11**, and **12**, see Supporting Information. X-ray crystal data for compounds **8**, **11**, and **12** are deposited at CCDC.[30]

NH-Imidazolines 5–8, and 12; Method A; General Procedure

Na (15 mg, 0.65 mmol) was added to a solution of carbonitrile (0.876 mmol) in anhyd MeOH (10 mL). The reaction mixture was stirred at 25 °C until TLC (SiO_2, EtOAc) or GC/MS showed total conversion of the carbonitrile into the imidate (usually 1–3 h). (1*R*,2*R*)-Cyclohexane-1,2-diamine (100 mg, 0.876 mmol), Et_3N (0.32 mL, 4.36 mmol), AcOH (3 drops) were added and the resulting solution was stirred at 40 °C for 12 h. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2, EtOAc–MeOH–aqNH_3, 1:1:0.01) to afford pure **5**–**8** and **12**.

(3a*R*,7a*R*)-2-(Pyridin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (5)

The title compound was synthesized from pyridine-2-carbonitrile (91 mg, 0.876 mmol); yield: 117 mg (66%); off-white solid; mp 110–112 °C; R_f = 0.37; $[\alpha]_D^{20}$ +141.6 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.32–1.41 (m, 2 H, CH_2), 1.54–1.58 (m, 2 H, CH_2), 1.81–1.84 (m, 2 H, CH_2), 2.30 (d, *J* = 10.9 Hz, 2 H, CH_2), 3.16–3.19 (m, 2 H, 2 × CH), 6.12 (br s, 1 H, NH), 7.31–7.34 (m, 1 H, Py), 7.73 (t, *J* = 7.8 Hz, 1 H, Py), 8.14 (d, *J* = 7.9 Hz, 1 H, Py), 8.54 (d, *J* = 4.8 Hz, 1 H, Py).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.19, 31.00, 71.10 (br), 122.17, 125.38, 136.78, 148.89, 148.92, 165.47.

EI-MS (70 eV): *m*/*z* (%) = 201 ($[M]^+$, 36), 172 (36), 159 (100), 146 (35), 105 (33), 78 (26).

Anal. Calcd for $C_{12}H_{15}N_3$ (201.27): C, 71.61; H, 7.51; N, 20.88. Found: C, 71.37; H, 7.29; N, 20.50.

(3a*R*,7a*R*)-2-(Pyrimidin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (6)

The title compound was synthesized from pyrimidine-2-carbonitrile (92 mg, 0.876 mmol); yield: 50 mg (31%); yellowish oil; mp 157–159 °C; R_f = 0.27; $[\alpha]_D^{20}$ +84.4 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.27–1.33 (m, 2 H, CH_2), 1.50–1.59 (m, 2 H, CH_2), 1.74–1.80 (m, 2 H, CH_2), 2.28 (d, *J* = 11.8 Hz, 2 H, CH_2), 3.14–3.20 (m, 2 H, 2 × CH), 5.05 (br s, 1 H, NH), 7.29 (t, *J* = 4.9 Hz, 1 H, Pm), 8.76 (d, *J* = 4.9 Hz, 2 H, Pm).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.09, 30.88, 70.48, 121.73, 157.49, 157.57, 164.01.

EI-MS (70 eV): *m*/*z* (%) = 202 ([M]$^+$, 19), 173 (42), 160 (100), 147 (50), 106 (28), 79 (16).

Anal. Calcd for $C_{11}H_{14}N_4$ (202.26): C, 65.32; H, 6.98; N, 27.70. Found: C, 65.14; H, 7.05; N, 27.42.

(3a*R*,7a*R*)-2-(Pyrazin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (7)

The title compound was synthesized from pyrazine-2-carbonitrile (92 mg, 0.876 mmol); yield: 170 mg (96%); off-white solid; mp 149–152 °C; R_f = 0.56; $[\alpha]_D^{20}$ +159.3 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.29–1.42 (m, 2 H, CH_2), 1.49–1.62 (m, 2 H, CH_2), 1.85 (t, *J* = 12.2 Hz, 2 H, CH_2), 2.20 (d, *J* = 11.0 Hz, 1 H, CH_2), 2.42 (d, *J* = 11.4 Hz, 1 H, CH_2), 3.11 (t, *J* = 12.5 Hz, 1 H, CH), 3.27 (t, *J* = 12.6 Hz, 1 H, CH), 6.09 (br s, 1 H, NH), 8.49–8.51 (m, 1 H, Pz), 8.61 (d, *J* = 2.4 Hz, 1 H, Pz), 9.37 (s, 1 H, Pz).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 24.25, 25.25, 30.35, 30.72, 66.33, 73.40, 142.93, 143.72, 144.01, 145.56, 163.10.

EI-MS (70 eV): *m*/*z* (%) = 202 ([M]$^+$, 27), 173 (33), 160 (100), 147 (36), 106 (25), 79 (14).

Anal. Calcd for $C_{11}H_{14}N_4$ (202.26): C, 65.32; H, 6.98; N, 27.70. Found: C 65.13; H, 6.65; N, 27.52.

1-((3a*R*,7a*R*)-3a,4,5,6,7,7a-Hexahydro-1*H*-benzo[*d*]imidazol-2-yl)isoquinoline (8)

The title compound was synthesized from isoquinoline-1-carbonitrile (135 mg, 0.876 mmol); yield: 8 mg (3%); off-white solid; mp 120–122; R_f = 0.63; $[\alpha]_D^{20}$ +31.6 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.37–1.42 (m, 2 H, CH_2), 1.58–1.67 (m, 2 H, CH_2), 1.87 (d, *J* = 8.5 Hz, 2 H, CH_2), 2.35 (br s, 2 H, CH_2), 3.29 (br s, 2 H, 2 × CH), 7.65–7.70 (m, 3 H, Isq), 7.81 (d, *J* = 7.4 Hz, 1 H, Isq), 8.48 (d, *J* = 5.6 Hz, 1 H, Isq), 9,62 (d, *J* = 8.8 Hz, 1 H, Isq).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 23.03, 25.30, 31.16, 31.85, 123.22, 126.89, 127.22, 128.55, 128.67, 130.51, 137.01, 141.21, 148.12, 165.98.

EI-MS (70 eV): *m*/*z* (%) = 251 ([M]$^+$, 41), 222 (24), 208 (100), 155 (40), 128 (45).

NH-Imidazolines 10, 13; Method B; General Procedure

To a suspension of imidate hydrochloride (0.876 mmol) in CH_2Cl_2 (10 mL) were added (1*R*,2*R*)-cyclohexane-1,2-diamine (100 mg, 0.876 mmol), Et_3N (0.32 mL, 4.36 mmol), and AcOH (3 drops) and the resulting solution was stirred at 25 °C for 48 h. The reaction was monitored on TLC (SiO_2, EtOAc) or GC/MS. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2, EtOAc–MeOH–aqNH_3, 1:1:0.01) to afford pure **9**–**11** and **13**.

(3a*R*,7a*R*)-2-(1*H*-Pyrrol-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (10)

The title compound was synthesized from methyl 1*H*-pyrrole-2-carbimidate hydrochloride (141 mg, 0.876 mmol); yield: 120 mg (72%); off-white solid; mp 309–312 °C; R_f = 0.24; $[\alpha]_D^{20}$ +45.0 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.21–1.30 (m, 2 H, CH_2), 1.47–1.49 (m, 2 H, CH_2), 1.78–1.80 (m, 2 H, CH_2), 2.25 (d, *J* = 11.6 Hz, 2 H, CH_2), 3.31–3.40 (m, 2 H, 2 × CH), 6.19 (s, 1 H, Pyr), 7.04 (s, 1 H, Pyr), 7.59 (s, 1 H, Pyr), 10.21 (s, 2 H, NH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 23.83, 28.82, 64.55, 111.69, 115.21, 120.08, 127.51, 158.84.

EI-MS (70 eV): *m*/*z* (%) = 189 ([M]$^+$, 95), 160 (30), 146 (100), 134 (22), 119 (13), 93 (39).

Anal. Calcd for $C_{11}H_{15}N_3$ (189.26): C, 69.81; H, 7.79; N, 21.65. Found: C, 69.65; H, 8.15; N, 21.39.

1,3-Bis((3a*R*,7a*R*)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazol-2-yl)benzene (13)

The title compound was synthesized from diethyl benzene-1,3-dicarbimidate dihydrochloride (257 mg, 0.876 mmol); yield: 104 mg (37%); off-white solid; mp 261–263 °C; R_f = 0.38; $[\alpha]_D^{20}$ +215.0 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.29–1.38 (m, 4 H, CH_2), 1.50–1.52 (m, 4 H, CH_2), 1.80–1.82 (m, 4 H, CH_2), 2.24 (d, *J* = 11.6 Hz, 4 H, CH_2), 3.08 (d, *J* = 6.9 Hz, 4 H, 2 × CH), 4.86 (br s, 2 H, NH), 7.35 (t, *J* = 7.8 Hz, Ben), 7.81 (d, *J* = 7.8 Hz, 2 H, Ben), 8.08 (d, *J* = 12.6 Hz, 1 H, Ben).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.15, 30.99, 69.81, 125.00, 128.83, 129.04, 131.11, 165.20.

EI-MS (70 eV): *m*/*z* (%) = 322 ([M]$^+$, 68), 293 (32), 279 (100), 267 (88), 226 (21), 182 (16), 129 (17).

Anal. Calcd for $C_{20}H_{26}N_4$ (322.45): C, 74.50; H, 8.13; N, 17.38. Found: C, 74.35; H, 8.24; N, 17.27.

N-Alkylation of Imidazolines 5–7 and 9–11; General Procedure

$LiN(SiMe_3)_2$ (1 M solution in THF, 0.51 mL, 0.51 mmol, 1.3 equiv) was added to a solution of imidazoline (0.392 mmol) in anhyd THF (10 mL) under argon at –20 °C. The resulting yellow solution was stirred for 30 min whereupon benzyl bromide (0.051 mL, 0.431 mmol, 1.1 equiv) in THF (5 mL) was added and the reaction mixture was stirred at 25 °C for an additional 3 h. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2, EtOAc–MeOH–aqNH_3, 1:1:0.01) to afford either imidazolines **14**–**16** and **20**–**22** or N,N′-disubstituted (1*R*,2*R*)-cyclohexane-1,2-diamines **17**–**19**.

(3a*R*,7a*R*)-1-Benzyl-2-(pyridin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (14)

The title compound was synthesized from imidazoline **5**, however, it could not be isolated in pure form. This product was detected only by GC/MS and decomposed to **17** during purification by column chromatography (see Supporting Information).

EI-MS (70 eV): *m*/*z* (%) = 291 ([M]$^+$, 100), 106 (84), 91 (78), 79 (28).

(3a*R*,7a*R*)-1-Benzyl-2-(pyrimidin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (15)

The title compound was synthesized from imidazoline **6** following the general procedure; yield: 36 mg (31%); off-white solid; mp 164–166 °C; R_f = 0.40; $[\alpha]_D^{20}$ +52.4 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.21–1.50 (m, 4 H, CH_2), 1.76–1.86 (m, 2 H, CH_2), 1.98 (d, *J* = 11.2 Hz, 1 H, CH_2), 2.30 (d, *J* = 11.1 Hz, 1 H, CH_2), 2.91 (t, *J* = 12.0 Hz, 1 H, CH), 3.18 (t, *J* = 12.0 Hz, 1 H, CH), 4.54–4.60 (m, 2 H, Bn), 7.18–7.27 (m, 5 H, Bn), 7.55 (t, *J* = 4.8 Hz, 1 H, Pm), 8.90 (d, *J* = 3.2 Hz, 2 H, Pm).

^{13}C NMR (100 MHz, CD_3OD): δ = 24.22, 25.30, 29.42, 30.76, 49.78, 70.26, 70.67, 122.06, 127.20, 127.75, 128.24, 137.50, 157.62, 159.12, 165.50.

EI-MS (70 eV): *m*/*z* (%) = 292 ([M]$^+$, 75), 237 (34), 201 (40), 159 (17), 106 (79), 91 (100).

(3a*R*,7a*R*)-1-Benzyl-2-(pyrazin-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (16)

The title compound was synthesized from imidazoline **7** following the general procedure; yield: 66 mg (46%); yellowish oil; R_f = 0.64; $[\alpha]_D^{20}$ +75.4 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.21–1.51 (m, 4 H, CH_2), 1.75–1.86 (m, 2 H, CH_2), 1.97 (d, *J* = 11.2 Hz, 1 H, CH_2), 2.32 (d, *J* = 10.8 Hz, 1 H, CH_2), 2.95 (t, *J* = 14.4 Hz, 1 H, CH), 3.22 (t, *J* = 14.4 Hz, 1 H, CH), 4.59 (d, *J* = 15.6 Hz, 1 H, Bn), 4.76 (d, *J* = 15.6 Hz, 1 H, Bn), 7.21–7.28 (m, 5 H, Bn), 8.67–8.68 (m, 2 H, Pz), 8.97 (s, 1 H, Pz).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.54, 26.58, 30.81, 32.06, 51.22, 71.92, 71.94, 128.55, 128.95, 129.61, 139.08, 145.03, 146.16, 146.96, 147.86, 165.77.

EI-MS (70 eV): *m*/*z* (%) = 292 ([M]$^+$, 94), 237 (16), 201 (14), 186 (13), 159 (9), 106 (84), 91 (100), 79 (15).

***N*-[(1*R*,2*R*)-2-(Benzylamino)cyclohexyl]pyridine-2-carboxamide (17)**

The title compound was synthesized from imidazoline **5** following the general procedure. This product was obtained after purification of **14** by column chromatography; yield: 57 mg (37%); yellowish oil; R_f = 0.62; $[\alpha]_D^{20}$ –30.0 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.27–1.42 (m, 4 H, CH_2), 1.75–1.78 (m, 2 H, CH_2), 1.97–1.99 (m, 1 H, CH_2), 2.13–2.15 (m, 1 H, CH_2), 2.61 (m, 1 H, C*H*NHBn), 3.65 (d, *J* = 13.2 Hz, 1 H, Bn), 3.85 (d, *J* = 13.2 Hz, 1 H, Bn), 3.91–3.95 (m, 1 H, C*H*NHCOPy), 7.17–7.25 (m, 5 H, Bn), 7.52 (t, *J* = 6.8 Hz, 1 H, Py), 7.94 (t, *J* = 7.6 Hz, 1 H, Py), 8.09 (d, *J* = 8.0 Hz, 1 H, Py), 8.63 (d, *J* = 4.4 Hz, 1 H, Py).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.78, 26.21, 32.12, 33.37, 51.21, 54.20, 61.03, 123.34, 127.86, 128.24, 129.54, 129.59, 138.93, 141.14, 149.81, 151.19, 166.87.

EI-MS (70 eV): *m*/*z* (%) = 309 ([M]$^+$, 2), 291 (25), 218 (16), 204 (28), 187 (60), 175 (33), 146 (24), 106 (64), 91(100), 78 (45).

Anal. Calcd for $C_{19}H_{23}N_3O$ (309.41): C, 73.76; H, 7.49; N, 13.58. Found: C, 73.85; H, 7.55; N, 13.69.

***N*-[(1*R*,2*R*)-2-(Benzylamino)cyclohexyl]pyrimidine-2-carboxamide (18)**

The title compound was synthesized from imidazoline **6** following the general procedure. This product was obtained after purification of **15** by column chromatography; yield: 46 mg (38%); yellowish oil; R_f = 0.56; $[\alpha]_D^{20}$ –19.6 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.29–1.48 (m, 4 H, CH_2), 1.77–1.82 (m, 2 H, CH_2), 2.01–2.03 (m, 1 H, CH_2), 2.18–2.21 (m, 1 H, CH_2), 2.65–2.70 (m, 1 H, C*H*NHBn), 3.69 (d, *J* = 12.8 Hz, 1 H, Bn), 3.90 (d, *J* = 12.8 Hz, 1 H, Bn), 3.93–3.99 (m, 1 H, C*H*NHCOPz), 7.19–7.29 (m, 5 H, Bn), 7.63 (t, *J* = 4.8 Hz, 1 H, Pm), 8.94 (d, *J* = 4.8 Hz, 1 H, Pm).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.81, 26.21, 31.97, 33.27, 49.78, 54.56, 61.00, 124.48, 128.37, 129.65, 129.69, 140.81, 158.97, 159.06, 165.09.

EI-MS (70 eV): *m*/*z* (%) = 310 ([M]$^+$, 6), 205 (28), 187 (51), 176 (36), 146 (24), 124 (20), 106 (17), 91 (100).

Anal. Calcd for $C_{18}H_{22}N_4O$ (310.39): C, 69.65; H, 7.14; N, 18.05. Found: C, 69.92; H, 7.24; N, 18.10.

***N*-[(1*R*,2*R*)-2-(Benzylamino)cyclohexyl]pyrazine-2-carboxamide (19)**

The title compound was synthesized from imidazoline **7** following the general procedure. This product was obtained after purification of **16** by column chromatography; yield: 54 mg (35%); off-white solid; mp 91–94 °C; R_f = 0.70; $[\alpha]_D^{20}$ –31.6 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.28–1.46 (m, 4 H, CH_2), 1.77–1.83 (m, 2 H, CH_2), 1.97–2.00 (m, 1 H, CH_2), 2.21–2.22 (m, 1 H, CH_2), 2.70–2.76 (m, 1 H, C*H*NHBn), 3.73 (d, *J* = 12.8 Hz, 1 H, Bn), 3.94 (d, *J* = 12.8 Hz, 1 H, Bn), 3.97 (m, 1 H, C*H*NHCOPz), 7.24–7.27 (m, 5 H, Bn), 8.69–8.70 (m, 1 H, Pz), 8.78 (d, *J* = 2.4 Hz, 1 H, Pz), 9.23 (d, *J* = 1.2 Hz, 1 H, Pz).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.74, 26.18, 31.68, 33.26, 50.88, 54.00, 61.02, 128.59, 129.73, 129.78, 140.09, 144.87, 144.97, 146.51, 148.64, 165.71.

EI-MS (70 eV): *m*/*z* (%) = 310 ([M]$^+$, 2), 219 (12), 187 (26), 176 (18), 146 (25), 106 (61), 91(100), 79 (28).

Anal. Calcd for $C_{18}H_{22}N_4O$ (310.39): C, 69.65; H, 7.14; N, 18.05. Found: C, 69.89; H, 7.30; N, 18.16.

(3a*R*,7a*R*)-1-Benzyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (20)

The title compound was synthesized from imidazoline **9** following the general procedure; yield: 84 mg (58%); yellowish oil; R_f = 0.42; $[\alpha]_D^{20}$ +31.2 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.20–1.47 (m, 4 H, CH_2), 1.72–1.75 (m, 1 H, CH_2), 1.80–1.87 (m, 2 H, CH_2), 2.28–2.31 (m, 1 H, CH_2), 2.76–2.82 (m, 1 H, C*H*NHBn), 3.14–3.17 (m, 1 H, C*H*NHCOPh), 4.13 (d, *J* = 16.4 Hz, 1 H, Bn), 4.50 (d, *J* = 16.0 Hz, 1 H, Bn), 7.22–7.30 (m, 5 H, Bn), 7.42–7.49 (m, 5 H, Ph).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.74, 26.63, 31.29, 32.29, 52.58, 71.59, 72.68, 128.56, 129.00, 129.71, 129.89, 131.45, 132.93, 139.32, 171.49 (1 signal is missing).

EI-MS (70 eV): *m*/*z* (%) = 290 ([M]$^+$, 56), 235 (38), 199 (21), 157 (35), 104 (20), 91 (100).

Anal. Calcd for $C_{20}H_{22}N_4$ (290.40): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.86; H, 7.70; N, 9.76.

(3a*R*,7a*R*)-1-Benzyl-2-(1*H*-pyrrol-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (21)

The title compound was synthesized from imidazoline **10** following the general procedure; yield: 96 mg (65%); off-white solid; mp 149–151 °C; R_f = 0.13; $[\alpha]_D^{20}$ +136.0 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.20–1.46 (m, 4 H, CH_2), 1.75–1.84 (m, 2 H, CH_2), 1.91–1.94 (d, 1 H, *J* = 10.1 Hz, CH_2), 2.27 (d, *J* = 8.0 Hz, 1 H, CH_2), 2.84 (t, *J* = 14.0 Hz, 1 H, C*H*NHBn), 3.15 (t, *J* = 13.6 Hz, 1 H, C*H*NHCOPyr), 4.50 (d, *J* = 16.4 Hz, 1 H, Bn), 4.79 (d, *J* = 16.4 Hz, 1 H, Bn), 6.14 (s, 1 H, Pyr), 6.41–6.42 (m, 1 H, Pyr), 6.94 (d, *J* = 0.8 Hz, 1 H, Pyr), 7.25–7.32 (m, 5 H, Bn).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.63, 26.50, 30.63, 32.22, 51.88, 70.77, 72.23, 110.38, 112.81, 122.00, 122.94, 128.31, 128.46, 129.80, 139.43, 163.47.

EI-MS (70 eV): *m*/*z* (%) = 279 ([M]$^+$, 100), 207 (46), 196 (78), 91 (89).

Anal. Calcd for $C_{18}H_{21}N_3$ (279.38): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.49; H, 7.50; N, 14.96.

(3a*R*,7a*R*)-1-Benzyl-2-(thiophen-2-yl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole (22)

The title compound was synthesized from imidazoline **11** following the general procedure; yield: 85 mg (59%); yellowish oil; R_f = 0.49; $[\alpha]_D^{20}$ +67.2 (*c* 0.5, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.21–1.48 (m, 4 H, CH_2), 1.75–1.84 (m, 2 H, CH_2), 1.92 (d, *J* = 12.0 Hz, 1 H, CH_2), 2.29 (d, *J* = 10.0 Hz, 1 H, CH_2), 2.92 (t, *J* = 14.8 Hz, 1 H, C*H*NHBn), 3.19 (t, *J* = 14.7 Hz, 1 H, CHNHCOTh), 4.42 (d, *J* = 16.4 Hz, 1 H, Bn), 4.74 (d, *J* = 16.4 Hz, 1 H, Bn), 7.09 (t, *J* = 4.0 Hz, 1 H, Th), 7.27–7.34 (m, 6 H, Bn + Th), 7.61 (d, *J* = 4.0 Hz, 1 H, Th).

^{13}C NMR (100 MHz, CD_3OD): δ = 25.59, 26.48, 30.88, 32.05, 52.13, 71.34, 72.77, 128.34, 128.62, 128.76, 129.86, 130.19, 130.24, 132.92, 139.18, 164.83.

EI-MS (70 eV): *m/z* (%) = 296 (M^+, 80), 241 (30), 205 (25), 163 (35), 110 (22), 91 (100).

Anal. Calcd for $C_{18}H_{20}N_2S$ (296.43): C, 72.93; H, 6.80; N, 9.45; S, 10.82. Found: C, 73.00; H, 6.74; N, 9.41; S, 10.71.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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