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Mloston, G; Rygielska, D; Jasinski, M; Heimgartner, H

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Abstract

A new exploration of some monoprotected derivatives of trans-1,2-diaminocyclohexane as a platform for the synthesis of enantiomerically pure imidazole derivatives is described. The primary amino group (-NH₂), present in the mono-imine derivative of salicylic aldehyde (hemi-salen derivative) 5 was used for sequential reactions with formaldehyde and a corresponding α-(hydroxyimino)ketone. (S)-(−)-1-Phenylethylamine was also used as starting material for the preparation of new imidazole N-oxides 7c and 10a-c, bearing a chiral N-(1-phenylethyl)carboxamido function at C(4). Imidazole N-oxides 10a-b possessing a Me or i-Pr group at N(1), respectively, follow the known sulfur-transfer pathway affording the corresponding imidazole-2-thiones 13a-b. However, in the case of imidazole N-oxide 10c with the bulky adamantan-1-yl substituent at N(1), the attempted ‘sulfur-transfer reaction’ led to the deoxygenated imidazole derivative 14. Finally, the same reaction with 7c, bearing the electron-withdrawing N-(1-phenylethyl)carboxamide residue at C(4) of the imidazole ring, yielded a mixture of deoxygenated imidazole 16 and imidazole-2-thione 15c.
Optically active imidazoles derived from enantiomerically pure trans-1,2-diaminocyclohexane

Grzegorz Młoston, a,* Dorota Rygielska, a,1 Marcin Jasiński, a,* Heinz Heimgartner b

a Department of Organic and Applied Chemistry, University of Łódź, Tamka 12, PL-91-403 Łódź, Poland
b Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

• Corresponding authors. Tel.: +48 42 635 57 61 (G. M.); + 48 42 635 5766 (M. J.); fax +48 42 665 5162; e-mails: gmloston@uni.lodz.pl; mjasinski@uni.lodz.pl

Dedicated to Professor Janusz Jurczak (Warsaw) on the occasion of his 70th birthday

Abstract—A new exploration of some monoprotected derivatives of trans-1,2-diaminocyclohexane as a platform for the synthesis of enantiomerically pure imidazole derivatives is described. The primary amino group (-NH2), present in the mono-imine derivative of salicylic aldehyde (hemi-salen derivative) 5 was used for sequential reactions with formaldehyde and a corresponding α-(hydroxyimino)ketone. (S)-(−)-1-Phenylethylamine was also used as starting material for the preparation of new imidazole N-oxides 7c and 10a−c, bearing a chiral N-(1-phenylethyl)carboxamido function at C(4). Imidazole N-oxides 10a−b possessing a Me or i-Pr group at N(1), respectively, follow the known sulfur-transfer pathway affording the corresponding imidazole-2-thiones 13a−b. However, in the case of imidazole N-oxide 10c with the bulky adamantyl-yl substituent at N(1), the attempted ‘sulfur-transfer reaction’ led to the deoxygenated imidazole derivative 14. Finally, the same reaction with 7c, bearing the electron-withdrawing N-(1-phenylethyl)carboxamide residue at C(4) of the imidazole ring, yielded a mixture of deoxygenated imidazole 16 and imidazole-2-thione 15c.

1. Introduction

Chiral 1,2-diamines are widely applied as easily available starting materials for the preparation of optically active heterocycles.2 Of special importance is trans-1,2-diaminocyclohexane (1a), which can be isolated as pure enantiomers by resolution via diastereomeric tartrates.3 In recent papers we reported the efficient synthesis of bis-imidazoles starting with enantiomerically pure 1a.4,5 The initially obtained N,N'-dioxides 2 were deoxygenated to give the bis-imidazoles 3, which subsequently were alkylated yielding the corresponding bis-imidazolium salts 4.6 Some of the optically active N,N'-dioxides as well as the deoxygenated bis-imidazoles were successfully applied as organocatalysts for the asymmetric alkylation of aromatic aldehydes7 and for asymmetric cyclopropanations.8

Figure 1. trans-1,2-Diaminocyclohexane (1a) (DACH) as a substrate for preparation of C2-symmetrical bis-imidazole derivatives 2a, 3a and 4a,b.

The goal of the present study was the synthesis of new series of optically active imidazole N-oxides using some monoprotected derivatives of 1a. Furthermore, the primarily obtained N-oxides should be converted into the corresponding imidazole-2-thiones. Both, imidazole N-oxides and imidazole-2-thiones are potentially attractive as new ligands for asymmetric synthesis or as organocatalysts. In numerous recent papers, some optically active azaaromatic N-oxides were demonstrated as efficient ligands.9a Moreover, it is well established that many thiourea derivatives, which can be considered as structural analogues of imidazole-2-thiones, act efficiently as organocatalysts and ligands for asymmetric synthesis.9b−c Nevertheless, to the best of our knowledge, no reports on the synthesis of optically active imidazole-2-thiones, potentially useful in asymmetric synthesis, are published to the date.
2. Results and discussion

Several methods for the monoprotection of 1a are known, and the most frequently applied are N,N-diethylation, N-acetylation, and N-Boc-protection. In addition to these methods, the conversion to a monoimine with aldehydes or ketones is also described, and this type of monoprotection with salicylic aldehydes is of special importance (hemi-salen-type ligands).

Based on a literature protocol, the desired monoinine 5 was prepared in high yield and, without purification, it was reacted with paraformaldehyde (Scheme 1). The obtained crude product was used for the condensation with α-hydroxyimino ketones 6 yielding, after heating for 8 h in ethanol, the desired imidazole 3-oxides 7 as crystalline materials. The enantiomeric purity of these products was proved by recording the $^1$H-NMR spectra with equimolar amounts of (S)-(−)-(tert-butyl) (phenyl)phosphinothioic acid (see Ref. 11a). In both cases, there was only one set of the diagnostic signals for H-C(2) and HC=N. For example, in the spectrum of 7a, these signals appeared at 9.70 and 8.13 ppm, respectively, and were significantly downfield shifted in comparison with the parent structure (7.82 and 8.00, respectively).

Recently, we described an efficient method for the preparation of 3-oxoimidazole-4-carboxamides using 2-hydroxyimino)-3-oxobutamide (8) was prepared by trapping of the in situ generated acetylketene with (S)-(−)-1-phenylethylamine (1b) and subsequent nitrosation of the β-oxoamide 9 (Scheme 2). In order to check the utility of 8 in the synthesis of enantiomerically pure 3-oxoimidazole-4-carboxamides 10, compound 8 was successfully employed in the reaction with N-methylidene amines (R = Me, i-Pr, Ad). Even in the case of the bulky N-(adamant-1-yl)formalimine (11e), the product 10c was obtained in fair yield.

The successful synthesis of N-oxides 10 prompted us to use 8 for the reaction with 5 in order to prepare the more complex hemi-salen-like imidazole 3-oxide 7c, possessing three stereogenic centres (Scheme 3).

As evidenced in a series of papers, 2-unsubstituted imidazole 3-oxides can be easily converted into the corresponding imidazole-2-thiones via sulfur-transfer reaction by treatment with 2,2,4,4-tetramethyl-3-thioxocyclobutaneone (12a) or the corresponding dithione 12b. The reaction mechanism involves a [2+3] cycloaddition reaction as an initiating step. Both thietiones 12a and 12b are easily available and in contrast to other representatives of this class of sulfur-containing substances, can be stored for a longer time without decomposition. Earlier studies indicated, that they act as efficient dipolarophiles and superior ‘sulfur transferring agents’ in reactions with 2-unsubstituted imidazole 3-oxides. With these 1,3-dipoles, they are more efficient than other popular thietiones, like thiobenzophenone or adamanthethione. According to the general ‘sulfur transfer’ protocol the new imidazole 3-oxides were treated with 12b in chloroform at room temperature. In the case of 10a,b, the reactions occurred smoothly yielding, as expected, imidazole-2-thiones 13a,b as sole products (Scheme 4). However, in the case of 10c, bearing the bulky adamantyl substituent at N(1), the deoxygenated imidazole 14 was obtained as the only product. A stepwise mechanism of the [2+3]-cycladdition reaction leading to deoxygenation of starting imidazole N-oxide, reacting as a ‘nitron-like’ 1,3-dipole, was extensively discussed in our earlier paper and an elusive oxathiirane, derived from 12b, was evidenced as an intermediate. In order to confirm the structure of the isolated product, imidazole 3-oxide 10c was reacted with freshly prepared Raney-nickel and imidazole 14 was isolated as sole product in 61% yield.

The reaction of dithione 12b with ‘hemi-salen derived’ imidazole 3-oxides 7a,b led to the expected imidazole-2-thiones 15a,b in good yields (Scheme 5). The presence of the electron-withdrawing carboxamide group at C(4) in 7c slightly influenced the reaction course, and along with imidazole-2-thione 15c, the deoxygenated imidazole 16 was formed. Both products were separated by column chromatography in 71% and 8% yield, respectively.
Surprisingly, in the $^1$H-NMR spectrum of 15c recorded in CDCl$_3$, two sets of diagnostic signals (in ca. 4:1 ratio) were found. An analogous doubled-signal pattern was observed in CD$_3$OD (ca. 3:1 ratio) as well as in DMSO-d$_6$ (ca. 5:3 ratio). The dynamic nature of 15c was proved by the registration of a series of $^1$H-NMR spectra in DMSO-d$_6$ at increased temperature (diagnostic part is shown in Figure 2). A likely explanation of the observed phenomena is the formation of two rotamers (s-(Z)-15c and s-(E)-15c) stabilized by strong intramolecular hydrogen bonding of the amide function (Scheme 6). The IR spectrum of 15c supports this assumption; in contrast to the corresponding imidazole N-oxide 7c ($\nu_{C=O}$ 1660 cm$^{-1}$) and the deoxygenated derivative 16 ($\nu_{C=O}$ 1653 cm$^{-1}$), in the case of 15c a significant shift of the amide C=O to 1629 cm$^{-1}$ is observed.

In addition, the synthesis of imidazole derivatives of 1, analogous to 7, was attempted starting with mono-Boc and mono-acetyl protected trans-1,2-diaminocyclohexane (1a) and the $\alpha$-(hydroxyimino)ketone 6a. In both cases, none of the expected imidazole N-oxides was obtained.

### 3. Conclusions

The results presented in this paper show that the monoimine 5, derived from trans-1,2-diaminocyclohexane and salicylaldehyde, is a suitable substrate for the preparation of non-symmetrical, enantiomerically pure imidazole N-oxides 7. On the other hand, optically active imidazole N-oxides with a carboxamide function at C(4) can be prepared using 2-hydroxyiminom-3-oxobutyramide 8, easily accessible from (S)–1-phenylethylamine (1b) and in situ generated acetylketene. Examples of both classes of N-oxides can be converted into the corresponding imidazole-2-thiones 13 and 15. However, in the cases of 10c and 7c, bearing an electron-withdrawing carboxamido group at C(4) and a bulky substituent at N(1), the deoxygenation of the imidazole N-oxide was observed. The described enantiomerically pure imidazole derivatives are potentially attractive ligands for asymmetric syntheses.

### 4. Experimental

#### 4.1. General

Melting points were determined in a capillary using a MEL-TEMP II apparatus (Aldrich) and are uncorrected. IR Spectra were recorded with a NEXUS FT-IR instrument as KBr pellets or as films; absorptions ($\nu$) are given in cm$^{-1}$. $^1$H NMR and $^{13}$C NMR Spectra were recorded on a BRUKER AVANCE III ($^1$H at 600 and $^{13}$C at 150 MHz) instrument in CDCl$_3$, CD$_3$OD or DMSO-d$_6$ solutions; chemical shifts ($\delta$) in ppm; coupling constants ($J$) in Hz. The multiplicity of the $^{13}$C signals was deduced from DEPT, supported by $^1$H-$^{13}$C HMQC spectra. Optical rotations were determined on a PERKIN-ELMER 241 MC polarimeter. ESI mass spectra were measured on a Finnigan MAT-95 instrument.

#### 4.2. Starting materials

Applied reagents such as racemic trans-1,2-diaminocyclohexane (technical grade), l-(-)-tartaric acid, salicylaldehyde, (S)–(-)-1-phenylethylamine, acetylacetone, 2,2,6-trimethyl-4H-1,3-dioxin-4-one, other ketones, alky amines, paraformaldehyde, and solvents are commercially available and were used as received. Enantiomerically pure (R,R)-trans-1,2-diamino-cyclohexane was prepared by the resolution of racemic DACH using natural tartaric acid.\textsuperscript{3} Formaldimines derived from methylamine, isopropylamine, and 1-adamanitameine were prepared according to literature protocols.\textsuperscript{19} $\alpha$-(Hydroxyiminom)ketones were obtained according to known procedures: Butane-2,3-dione monooxime by nitrosation of butanone using isoamyl nitrite;\textsuperscript{19} 1,2-diphenylethane-1,2-dione monooxime (benzil monooxime) from dibenzoyl and hydroxylamine.\textsuperscript{18} Monooimine 5\textsuperscript{18} was obtained in 90% yield (95% purity) and used in the next step without further purification.

#### 4.3. Synthesis of imidazole 3-oxides 7a-c

To the magnetically stirred solution of monooimine 5 (10.0 mmol, 2.2 g) in dry ethanol (30 mL), containing
freshly activated molecular sieves 4Å, paraformaldehyde (11.0 mmol, 0.33 g) was added in one portion at 0 °C. The resulting mixture was allowed to reach r.t. and stirred overnight. Next, the respective α-hydroxyimino)ketone (11.0 mmol; 1.11 g of 6a, 2.48 g of 6b, or 2.57 g of 8) was added and the mixture refluxed for 8 h. After the solution was cooled and filtered, the solvent was removed in vacuo, the oily residue was purified by column chromatography (CC) to give the product of type 7 as yellow solid.

4.3.1. Imidazole-3-oxide 7a

Yield after CC (SiO2, AcOEt then AcOEt/MeOH 1:1, Rf = 0.36): 1.60 g (51%). Yellow solid. Mp 139–141 °C.

4.3.2. Imidazole-3-oxide 7b

Yield after CC (SiO2, AcOEt then AcOEt/MeOH 1:1, Rf = 0.74): 1.88 mg (43%). Yellow solid. Mp 117–120 °C.

4.3.3. Imidazole-3-oxide 7c

Yield after CC (SiO2, AcOEt then AcOEt/MeOH 6:1, Rf = 0.54): 2.05 g (46%). Yellow solid. Mp 99–102 °C. IR (KBr): 3420 vs (br.), 2935 s, 2860 m, 1628 vs, 1578 m, 1497 m, 1452 m, 1416 m, 1340 m, 1279 m, 1208 m, 1197 m, 1158 m, 1129 m, 1088 m, 1044 m, 1004 m, 963 m, 916 m, 891 m, 875 m, 840 m, 821 m (OH). 1H NMR (CDCl3): 12.70 (s, 1H, OH); 8.00 (s, 1H, –N=CH–); 7.82 (s, 1H, H); 7.30–7.28 (m, 1 arom. H); 5.15 (s, 1H, Me). 13C NMR (CDCl3): 199.6 (s, C=O); 162.6 (s, CONH); 139.3, 138.9, 139.0, 132.3 (3s, 3C); 127.0, 126.9, 126.0 (2C), 119.0, 118.9, 116.7 (6d, 6CH); 117.9–117.0 (m, 2 arom. H); 7.19-7.17 (m, 1 arom. H); 7.10 (dd, J = 7.2, 1H); 2.50 (s, 3H, Me); 2.12–2.06 (m, 1H, H); 1.63–1.56 (m, 1H, CHx); 1.49–1.41 (m, 1H, CHx); 1.37–1.30 (m, 1H, CHx). 13C NMR (CDCl3): 615.7 (s, –N=CH–); 160.5 (s, (Ph)C=O); 132.8, 130.2, 130.9 (2C), 129.6, 129.5 (2C), 129.1 (2C), 128.0, 127.9 (2C), 119.0, 119.0 (10d, 14CH(Ph)); 128.1, 127.1, 126.5, 125.6, 118.3 (5s, 5CH3); 123.2 (d, C(2)); 72.9, 59.9 (2d, CH2(3)); 34.0, 33.3, 24.9, 23.6 (4t, 4CH2(3c)); ESI-HRMS: 438.2174 (cald. 438.2176 for C22H24N4O3, [M+Na]+). [α]D25 = −81.2 (c 1.05, MeOH).

4.3.4. Synthesis of (S)-(−)-N-(1-phenylethyl)-2-hydroxyimino-3-oxobutramide (8)

A mixture of (S)-(−)-1-phenylethylamine (1b, 6.61 g, 54.6 mmol) and 2,2,6-trimethyl-4-formalimine (11.0 mmol) was added and the mixture refluxed for 8 h. After the solution was cooled and filtered, the solvent was removed in vacuo, the residue was flash chromatographed (SiO2, AcOEt/CHCl3 6:1, Rf = 0.37) to give crude β-oxoamide 9 (10.82 g, 96 %) as pale orange oil, which was used in the next step without further purification. The amide 9 (10.82 g, 52.8 mmol) was dissolved in glacial AcOH (25.0 mL), the resulting mixture was magnetically stirred while cooling (water/ice bath), and a solution of sodium nitrite (4.9 g, 71.1 mmol) in H2O (7.0 mL) was added dropwise. After ca. 2.5 h, the mixture was diluted with H2O (90 mL) and extracted with three portions of CHCl3 (70 mL each). The combined organic phases were washed with a saturated aqueous solution of NaHCO3, then with water, dried with MgSO4, and the solvent removed. The crude product was flash chromatographed (SiO2, CH2Cl2) and purified by CC (SiO2, petroleum ether/Et2O 7:1, Rf = 0.25) to give 8 (6.52 g) as a pale yellow oil in 51 % overall yield. IR: 3281 vs (br.), 2980s, 1686s, 1648s, 1551s, 1469m, 1451m, 1416m, 1363m, 1107m, 1019m, 700m. 1H NMR (CDCl3): 9.39 (br. s, 1H, NH); 7.38–7.35 (m, 2 arom. H); 7.32–7.28 (m, 3 arom. H); 5.15 (quint, J = 7.2, 1H); 2.50 (s, 3H, Me); 1.57 (d, J = 7.2, Me). 13C NMR (CDCl3): 199.6 (s, C=O); 162.6 (s, CONH); 143.4 (s, C=N); 141.6 (s, C(Ph)); 128.9, 127.8, 126.0 (3d, S(Ph)); 48.7 (d, CH); 26.2, 21.9 (2q, 2Me). ESI-HRMS: 257.0894 (cald. 257.0896 for C12H14N2NaO3, [M+Na]+).

4.4. Synthesis of (S)-(−)-N-(1-phenylethyl)-1,5-dimethyl-3-oxide-1H-imidazole-4-carboxamide (10a)

A solution of (S)-(−)-1-phenylethylamine (11b, 1.91 g, 10.0 mmol) and the respective formaldimine 11 (12.0 mmol) in ethanol (30 mL) was refluxed for 5 h. After the solvent was removed, the residue was washed with Et2O (3 portions of ca. 20 mL) and purified by recrystallization (10a) or chromatography (10b).

4.5. Synthesis of imidazole-3-oxides 10a and 10b

A solution of (S)-(−)-1-phenylethyl-2-hydroxyimino-3-oxobutramide (8, 2.34 g, 10.0 mmol) and the respective formaldimine 11 (12.0 mmol) in ethanol (30 mL) was refluxed for 5 h. After the solvent was removed, the residue was washed with Et2O (3 portions of ca. 20 mL) and purified by recrystallization (10a) or chromatography (10b).
11.15 (br. d,  J = 6.6, 1H, CONH); 7.74 (s,  1H, HC(2)); 7.40-7.39 (m, 2 arom. H); 7.33-7.30 (m, 2 arom. H); 7.22-7.20 (m, 1 arom. H); 5.27 (quint,  J = 7.2, 1H); 3.55 (s, 3H, MeN); 2.59 (s, 3H, Me); 1.57 (d,  J = 7.2, 3H, Me). 13C NMR (CDCl3): 158.6 (s,  C=O); 143.8, 130.6, 125.2 (3s, C(Ph)); 124.5, 123.9, 128.3, 128.7, 126.8, 125.6, 124.8, 123.0, 122.4, 121.4, 111.7, 109.0, 108.0, 106.0, 105.6, 105.4, 105.3 (s, C(Ph), C(4)); 138.5, 126.8, 126.1 (3d, 5CH(Ph)); 60.6 (s,  N-C(Ad)); 48.3 (d,  CH); 41.9, 29.6 (2t, 6CH2, Ad); 35.5 (d, 3CH3, Ad); 23.0, 13.2 (2q, 2Me). ESI-HRMS: 402.2152 (calcld. 402.2152 for C23H29N3NaOS, [M+Na]+). 380.2331 (calcld. 380.2323 for C21H19N3O2S, [M+H]+). [a]D^25 = -6.4 (c 5.00, CHCl3).

4.7. Reactions of imidazole 3-oxides of type 7 and 10 with 2,2,4,4-tetramethylcyclobutane-1,3-dithione (12b)

To the magnetically stirred solution of an imidazole N-oxide 7a-c or 10a-c (1.0 mmol) in CHCl3 (5 mL), excess 2,2,4,4-tetramethylcyclobutane-1,3-dithione (12b, 1.8 mmol, 309 mg) in CHCl3 (3 mL) was added dropwise at 0 °C, and stirring was continued overnight, at r.t. Then, the solvent was removed under reduced pressure, the resulting material was purified and identified as the corresponding imidazole-2-thione (13 or 15) and/or as an imidazole (14 and 16).

4.7.1. (S)-N-(1-Phenylethyl)-1,3-dihydro-1,5-dimethyl-2(3H)-thioimidazolide-4-carboxamide (13a)

Yield: 98 mg (36%). Colorless crystals. Mp 221–223 °C (EtOH). IR (KBr): 3312vs, 3166vs (br.), 1661s, 1626m, 1537m, 1487m, 1475m, 1450m, 1425m, 1395m, 1368m, 1367m, 702m. 1H NMR (CDCl3): 12.83 (br. s, 1H, NH); 7.48 (br. d,  J = 7.8, 1H, NH); 7.30-7.28 (m, 2 arom. H); 7.23-7.20 (m, 2 arom. H); 7.16-7.13 (m, 1 arom. H); 5.16 (quint,  J = 7.2, 1H); 3.41 (s, 3H, Me); 2.42 (s, 3H, Me); 1.51 (d,  J = 6.6, 3H, Me). 13C NMR (CDCl3): 158.9, 157.5 (2s,  C=O, C=S); 143.2, 143.1, 118.7 (3s, C(Ph), C(4), C(5)); 128.5, 127.2, 126.4 (3d, 5CH(Ph)); 49.3 (d,  CH); 31.0, 22.1, 10.2 (3q, 3 Me). ESI-HRMS: 298.0986 (calcld. 298.0984 for C13H18N3NaOS, [M+Na]+). [a]D^25 = +326.3 (c 0.80, CHCl3).

4.7.2. (S)-(1-Phenylethyl)-1,3-dihydro-1-isopropyl-5-methyl-2(3H)-thioimidazolide-4-carboxamide (13b)

Yield after CC (SiO2, AcOEt/MeOH 1:1, Rf = 0.65); 173 mg (56%). Colorless crystals. Mp 107–110 °C (IR (KBr): 3304vs (br.), 3061m, 2973m, 2933m, 1656m, 1626s, 1540m, 1494s, 1451m, 1416m, 1370m, 1282m, 1197m, 763m, 700m. 1H NMR (CDCl3): 13.11 (br. s, 1H, NH); 7.62 (br. d,  J = 7.2, 1H, NH); 7.38-7.37 (m, 2 arom. H); 7.30-7.28 (m, 2 arom. H); 7.23-7.20 (m, 1 arom. H); 5.30 (br. s, 1H, iPr); 5.23 (quint,  J = 7.2, 1H); 2.64 (s, 3H, Me); 1.57 (d,  J = 7.2, 3H, Me); 1.52-1.49 (m, 6H, iPr). 13C NMR (CDCl3): 158.0 157.7 (2s,  C=O, C=S); 143.4, 143.0, 119.3 (3s, C(Ph), C(4), C(5)); 128.5, 127.2, 126.3 (3d, 5CH(Ph)); 49.5, 49.2 (2d, 2CH); 22.1, 20.4, 11.1 (3q, 4 Me). ESI-HRMS: 326.1299 (calcld. 326.1297 for C13H18N3NaOS, [M+Na]+). [a]D^25 = +149.0 (c 1.00, CHCl3).

4.7.3. (S)-(1-Phenylethyl)-1-adamantyl-5-methylimidazolide-4-carboxamide (14)

Yield after CC (SiO2, AcOEt/CHCl3 1:2, Rr = 0.70); 203 mg (56%). Colorless solid. Mp 132–134 °C (IR (KBr): 3407m, 2910s, 2856m, 1660v, 1578s, 1494v, 1452m, 1235m, 697m. 1H NMR (CDCl3): 7.59 (br. s, 1H, NH); 7.51 (s, 1H, HC(2)); 7.40-7.38 (m, 2 arom. H); 7.33-7.29 (m, 2 arom. H); 7.23-7.20 (m, 1 arom. H); 5.25 (quint,  J = 7.2, 1H); 2.86 (s, 3H, Me); 2.25 (br. s, 3H, 3CH3, Ad); 2.21 (d,  J = 2.4, 6H, CH2, Ad); 1.80-1.73 (m, 6H, CH2, Ad); 1.56 (d,  J = 7.2, 3H, Me). 13C NMR (DMSO-d6): 162.9 (s,  C=O); 145.1, 132.2, 131.5 (3s, C(Ph), C(4), C(5)); 133.6 (d,  C(2)); 128.4 (2C), 126.7, 126.2 (2C) (3d, 5CH(Ph)); 57.9 (s, N-C(Ad)); 47.4 (d,  CH); 41.5, 29.2 (2t, 6CH2, Ad); 35.4 (d, 3CH3, Ad); 22.4, 12.8 (2q, 2Me). ESI-HRMS: 386.2200 (calcld. 386.2203 for C23H29N3NaOS, [M+Na]+).
4.7.3. 1H NMR (CDCl$_3$): 5.47-5.43 (m, 1H, $J = 8.4$, 1 arom. H); 6.75 (t, $J = 7.2$, 1 arom. H); 5.19-5.15 (m, 1H, cHex); 3.86-3.81 (m, 1H, cHex); 3.31-3.24 (m, 1H, cHex); 1.91, 1.85 (2s, 6H, 2Me); 1.76-1.51 (m, 6H, cHex); 1.36-1.28 (m, 1H, cHex).

13C NMR (CDCl$_3$): 157.2 (s, (Ph)C -OH); 160.6 (s, CONH); 143.8, 132.6, 131.7, 118.9, 118.4 (3s, C(Ph), C(4), C(5)); 64.9, 61.6 (2d, 2CH(cHex)); 34.5, 27.2, 25.6, 23.7 (4t, 4CH$_2$(cHex)); 9.2, 9.0 (2q, 2Me). ESI-HRMS: 435.2167 (calc. 435.2162 for C$_{25}$H$_{28}$N$_3$O$_2$S, $[M+Na]^{+}$).

Yield after CC (SiO$_2$, AcOEt/CHCl$_3$ 1:1, isolated as more polar fraction, $R_f = 0.44$): 34 mg (8%). Yellow semi-solid. IR (KBr): 1630, 1582, 1494s, 1449m, 1278m, 1229m, 758m, 700m.

1H NMR (CDCl$_3$): 12.65 (s, 1H, OH); 7.91 (s, 1H, – N=CH–); 7.40 (s, 1H, H(2C)); 7.33-7.28 (m, 2 arom. H); 7.26-7.24 (m, 3 arom. H); 7.21-7.18 (m, 1 arom. H); 7.01 (dd, $J = 7.6$, $J = 1.6$, 1 arom. H); 6.87 (dd, $J = 8.1$, 1 arom. H); 6.76 (dt, $J = 7.4$, $J = 1.1$, 1 arom. H); 5.19 (quint, $J = 7.1$, 1H, H(1)); 4.06-4.01 (m, 1H, cHex); 3.36 (dt, $J = 10.5$, $J = 4.4$, 1H, cHex); 2.51 (3H, Me); 2.14-2.11 (m, 1H, cHex); 2.02-1.75 (m, 6H, cHex); 1.54-1.49 (m, 3H, 1H, cHex) (calc. 485.1985 for C$_{25}$H$_{28}$N$_3$O$_2$S, $[M+Na]^{+}$).

The crude mixture was filtered through Celite® pad, as a colorless solid. 13C NMR (CDCl$_3$): 163.5 (s, –N=CH–); 162.8 (s, (Ph)-COH); 160.4 (s, CONH); 138.9, 131.7, 128.7, 128.1, 127.8, 127.5, 124.9, 116.8, 116.8 (12d, 14CH(Ph)); 64.8, 62.1 (2d, CH$_2$(cHex)); 34.4, 27.7, 25.3, 23.7 (4t, 4CH$_2$(cHex)). ESI-HRMS: 454.1949 (calc. 454.1948 for C$_{25}$H$_{32}$N$_2$O$_2$, $[M+H]^{+}$).

4.7.4. Imidazole 16

Yield after CC (SiO$_2$, AcOEt/CHCl$_3$ 1:1, isolated as more polar fraction, $R_f = 0.44$): 34 mg (8%). Yellow semi-solid. IR (KBr): 364.2384 (calc. 364.2383 for C$_{25}$H$_{32}$N$_2$O$_2$, $[M+H]^+$). $[\alpha]_D^{25} = -33.0 (c 1.00, CHCl$_3$).

4.8. Deoxygenation of 10c with Raney-nickel

To the solution of 10c (101 mg, 0.26 mmol) in methanol (8.0 mL) a suspension of freshly prepared Raney-Ni in methanol was added in small portions at r.t., until the starting material was fully consumed (TLC monitoring). The crude mixture was filtered through Celite® pad, washed with MeOH, and the solvent was removed from the filtrate. The resulting residue was purified on preparative TLC plates (SiO$_2$) using CHCl$_3$/AcOEt mixture (2:1) to give 58 mg (61%) of 14 as a colorless solid.

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References