Synthesis of 2-Hydroxymethyl-1*H*-imidazoles from 1,3-Dihydroimidazole-2-thiones

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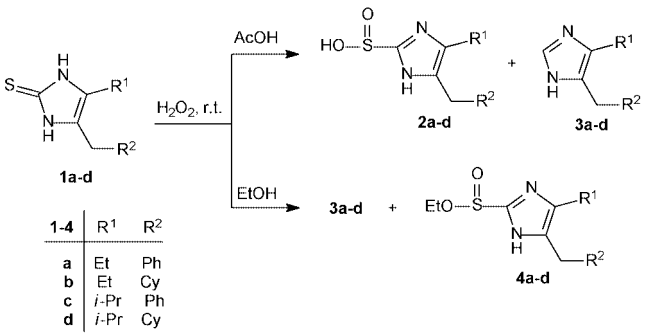
Abstract: 1,3-Dihydroimidazole-2-thiones **1a**–**d** were desulfurized by hydrogen peroxide in either acid or neutral medium to afford 1*H*-imidazoles **3a**–**d**. Reaction of **3b**,**d** with dimethylsulfamoyl chloride furnished *N*,*N*-dimethylsulfamoylimidazoles **5** and **6a**,**b**. Lithiation of **5** and **6a**,**b** followed by formylation and reduction yielded the 2-hydroxymethyl derivatives **7** and **8a**,**b**. 4-Alkyl-5-cyclohexylmethyl-1*H*-imidazol-2-yl)methanols **9a**,**b** were obtained by hydrolysis of **7** and **8a**,**b**.

Key words: 1,3-dihydroimidazole-2-thiones, desulfurization, imidazole-2-sulfinic acids, 2-hydroxymetylimidazoles

Desulfurization of sulfur-containing compounds, including thioureas, has been achieved by using a number of different reagents. Raney nickel has being the most often employed;[1] other methods involved the use of nickel-sodium hydride complexes[2] and transition metal compounds,[3] alkali bromates and iodates,[4] nitric acid,[5] potassium superoxide,[6] oxygen and potassium *tert*-butoxide,[7] ozone,[8] 3,3-dimethyldioxirine,[9] and a photochemical reaction involving singlet oxygen.[10,11] Alkaline hydrogen peroxide has been used for the oxidation of pyrimidine-2-thiones to the corresponding sulfinic acids. Subsequent refluxing of the isolated sulfinic acids with sulfuric acid afforded the desulfinated pyrimidines.[12] Alkaline hydrogen peroxide and sodium peroxide have also been used for the conversion of thioureas into ureas.[13] In this work, hydrogen peroxide was used for the desulfurization reaction of 1,3-dihydroimidazole-2-thiones in acid and neutral medium followed by hydroxymethylation at the 2-position. 2-(Hydroxymethyl)imidazoles are interesting starting materials and have been used in a practical synthesis of immunosuppressant compounds.[14]

4-Benzyl-5-ethyl-1,3-dihydroimidazole-2-thione (**1a**) has been previously synthesized by Bullerwell and Lawson,[15] 4-benzyl-5-isopropyl-1,3-dihydroimidazole-2-thione (**1c**)[16] and 5-alkyl-4-cyclohexyl-1,3-dihydroimidazole-2-thiones **1b**,**d**[17] have been synthesized by Loksha et al.[16,17] In the present investigation we found that treatment of 1,3-dihydroimidazole-2-thiones **1a**–**d** with hydrogen peroxide in an acidic medium afforded 1*H*-imidazole-2-sulfinic acids **2a**–**d** as the major products and the desulfurized imidazoles **3a**–**d** as the minor products. Treating compounds **1a**–**d** with hydrogen peroxide in a neutral medium in ethanol furnished the desulfurized imidazoles **3a**–**d** as the major products and the ethyl esters of 1*H*-imidazole-2-sulfinic acids **4a**–**d** as the minor products. The imidazole-2-sulfinic acids **2a**–**d** are somewhat stable in acidic medium and only small amounts were converted to the desulfinated imidazoles **3a**–**d** through elimination of sulfur dioxide which is further oxidized to sulfuric acid by an excess of hydrogen peroxide. Under neutral reaction conditions in ethanol, small amounts of the initially formed sulfinic acids were esterified by the solvent to compounds **4a**–**d**, whereas the major part of the sulfinic acids were converted to compounds **3a**–**d** (Scheme 1). 5-Benzyl-4-ethyl-1*H*-imidazole (**3a**) has been previously synthesized by Bredereck et al.[18] by an independent route through condensation of 4-benzyl-5-ethyloxazole with formamide.



Scheme 1

In order to activate the imidazole ring toward lithiation reactions, 4-alkyl-5-cyclohexylmethyl-1*H*-imidazoles **3b**,**d** were reacted with dimethylsulfamoyl chloride in toluene in the presence of triethylamine. Coupling at N-1 or N-3 occurred when R^1 was an ethyl group, while coupling occurred only at N-1 when R^1 was an isopropyl group due to steric hindrance of the isopropyl group. Each of the compounds **5** and **6a**,**b** were lithiated at the 2-postion of the imidazole ring by treatment with *n*-butyl lithium at 78 °C. Subsequent formylation using dimethylformamide afforded the 2-formyl derivative which without isolation was immediately reduced by sodium borohydride to furnish 4-cyclohexylmethyl-5-ethyl-2-hydroxymethyl-imidazole-1-sulfonic acid dimethylamide (**7**) and 4-alkyl-5-

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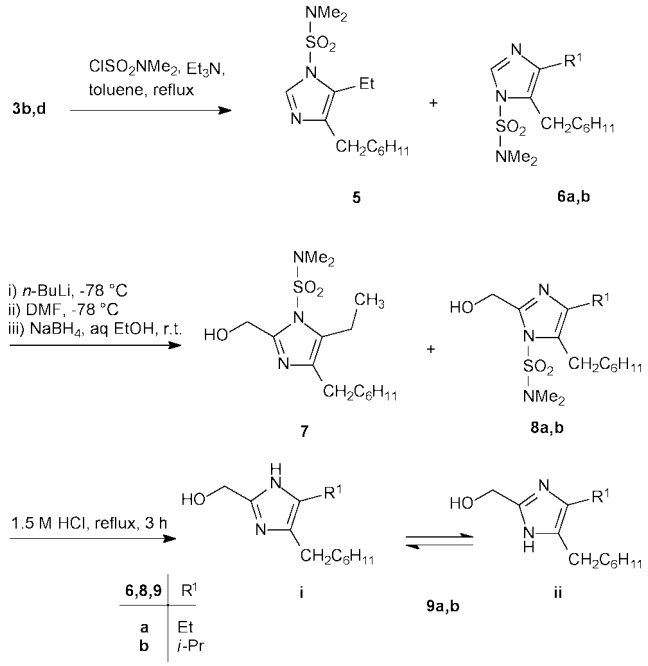
cyclohexylmethyl-2-hydroxymethylimidazole-1-sulfonic acid dimethylamides **8a**,**b**. For the compounds **5** and **6** and for **7** and **8**, respectively, the structural assignment was also based on R_f values from TLC on silica. Besides the above-mentioned influence of sterical hindrance on the formation of **6b**, we have previously observed smaller R_f values for 4,5-disubstituted imidazoles when the more lipophilic substituent was next to an N1 substituent and larger R_f values for the compounds with the interchanged 4- and 5-substituents.[17] 5-(Cyclohexylmethyl-4-ethyl-1*H*-imidazol-2-yl)methanol (**9a**) was obtained by either hydrolysis of 4-cyclohexylmethyl-5-ethyl-2-hydroxymethylimidazole-1-sulfonic acid dimethylamide (**7**) or 5-cyclohexylmethyl-4-ethyl-2-hydroxymethylimidazole-1-sulfonic acid dimethylamide (**8a**) in an acidic medium (1.5 M hydrochloric acid), while acid hydrolysis of compound **8b** afforded (5-cyclohexylmethyl-4-isopropyl-1*H*-imidazol-2-yl)methanol (**9b**) (Scheme 2).



Scheme 2

Compounds **9a**,**b** are believed to exist in a rapid equilibrium between the two tautomeric forms **i** and **ii** which explains why C-4 and C-5 could not be detected in ^{13}C NMR.

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C with TMS as the internal standard. Cy denotes cyclohexyl. EIMS were recorded on a Finnigan Mat SSQ 701 spectrometer, MALDI spectra were recorded on a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points were determined on a Büchi melting point apparatus. Elementary analyses were performed at H.C. Ørsted Institute, University of Copenhagen. Silica gel (0.040–0.063 mm) used for column chromatography and analytical silica gel TLC plates 60 F_{254} were purchased from Merck. Solvents for column chromatography were distilled prior to use.

1*H*-Imidazole-2-sulfinic Acids 2a–d and 1*H*-Imidazoles 3a–d, Method A; General Procedure

To a solution of each of the compounds **1a**–**d** (5 mmol) in HOAc (20 mL), 35% H_2O_2 (1.5 mL, 15 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 2 h. The solid product formed was filtered off, and dried in vacuo affording the imidazole-2-sulfinic acids **2a**–**d**. The filtrate was evaporated in vacuo till dryness, H_2O (20 mL) was added to the residue, the solution was neutralized with a 10% aq solution of $NaHCO_3$, and extracted with EtOAc (3 × 20 mL). The EtOAc extracts were collected, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residual material was dried to afford compounds **3a**–**d**.

5-Benzyl-4-ethyl-1*H*-imidazole-2-sulfinic Acid (2a)

Yield: 0.6 g (48%); mp 276–278 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.08 (t, 3 H, J = 7.3 Hz, CH_3CH$_2$), 2.61 (q, 2 H, J = 7.3 Hz, CH$_3$CH_2), 3.96 (s, 2 H, CH_2Ph), 7.22–7.33 (m, 5 H, Ph), 14.58 (br s, 1 H, OH).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 13.66 (*C*H$_3$CH$_2$), 16.45 (CH$_3$*C*H$_2$), 28.66 (*C*H$_2$Ph), 126.84 (C-4), 126.59, 128.17, 128.57, 137.88 (C$_{arom}$), 130.72 (C-5), 145.95 (C-2).

MALDI MS: m/z = 273 (100%, M + Na$^+$)

Anal. Calcd for $C_{12}H_{14}N_2O_2S{\cdot}0.25H_2SO_4$ (274.84): C, 52.44; H, 5.32; N, 10.19. Found: C, 52.66; H, 5.08; N, 10.25.

5-Cyclohexylmethyl-4-ethyl-1*H*-imidazole-2-sulfinic Acid (2b)

Yield: 0.72 g (56%); mp 290–292 °C.

^1H NMR (DMSO-d_6): δ = 0.86–0.98 (m, 2 H, H$_{cy}$), 1.13–1.50 (m, 6 H, CH_3CH$_2$ and H$_{cy}$), 1.55–1.65 (m, 6 H, H$_{cy}$), 2.45 (d, 2 H, J = 5.8 Hz, CH_2Cy), 2.56 (q, 2 H, J = 7.3 Hz, CH$_3$CH_2), 14.38 (br s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 13.79 (CH_3CH$_2$), 16.48 (CH$_3$*C*H$_2$), 25.47, 25.72, 32.04, 37.39 (C$_{cy}$), 30.17 (*C*H$_2$Cy), 126.68 (C-4), 130.52 (C-5), 145.68 (C-2).

Anal. Calcd for $C_{12}H_{20}N_2O_2S{\cdot}0.25H_2SO_4$ (280.89): C, 51.31; H, 7.36; N, 9.97. Found: C, 51.43; H, 7.14; N, 9.92.

5-Benzyl-4-isopropyl-1*H*-imidazole-2-sulfinic Acid (2c)

Yield: 0.81 g (61%); mp 285–278 °C.

^1H NMR (DMSO-d_6): δ = 1.18 [d, 6 H, J = 6.5 (CH_3)$_2$CH], 3.16 [hept, 1 H, J = 6.5 Hz, (CH$_3$)C*H*], 3.98 (s, 2 H, CH_2Ph), 7.20–7.32 (m, 5 H, Ph), 14.56 (br s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 21.28 [(*C*H$_3$)$_2$CH], 23.69 [(CH$_3$)$_2$*C*H], 28.68 (*C*H$_2$Ph), 125.75 (C-4), 126.58, 128.07, 128.58, 138.03 (C$_{arom}$), 134.78 (C-5), 146.40 (C-2).

Anal. Calcd for $C_{13}H_{16}N_2O_2S{\cdot}0.25H_2SO_4$ (288.87): C, 54.05; H, 5.76; N, 9.70. Found: C, 54.20, H, 5.60; N, 9.73.

5-Cyclohexylmethyl-4-isopropyl-1*H*-imidazole-2-sulfinic Acid (2d)

Yield: 0.88 g (65%); mp 295–297 °C.

^1H NMR (DMSO-d_6): δ = 0.85–0.99 (m, 2 H, H$_{cy}$), 1.11–1.31 [m, 9 H, (CH_3)$_2$CH and H$_{cy}$], 1.541.68 (m, 6 H, H$_{cy}$), 2.47 (d, 2H, J = 6.3 Hz, CH_2Cy), 3.05 [hept, 1 H, J = 6.9 Hz, (CH$_3$)$_2$C*H*].

^{13}C NMR (DMSO-d_6): δ = 21.56 [(*C*H$_3$)$_2$CH], 23.73 [(CH$_3$)$_2$*C*H], 25.48, 25.73, 32.05, 37.51 (C$_{cy}$), 30.30 (*C*H$_2$Cy), 125.64 (C-4), 134.72 (C-5), 146.20 (C-2).

Anal. Calcd for $C_{13}H_{22}N_2O_2S{\cdot}0.45H_2SO_4$ (314.53): C, 49.64; H, 7.34; N, 8.91. Found: C, 49.46; H, 7.06; N, 8.79.

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5-Benzyl-4-ethyl-1*H*-imidazole (3a)
Yield: 12% (method A), 48% (method B); mp 106–108 °C (Lit.[18] mp 106 °C).

^{1}H NMR (DMSO-d_6): δ = 1.07 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 2.49 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 3.79 (s, 2 H, C*H*$_2$Ph), 7.11–7.27 (m, 5 H, Ph), 7.40 (s, 1 H, H-2).

^{13}C NMR (DMSO-d_6): δ = 14.59 (*C*H$_3$CH$_2$), 18.01 (CH$_3$*C*H$_2$), 31.35 (*C*H$_2$Ph), 125.56, 128.06, 128.14, 132.99 (C$_{arom}$), 141.02 (C-2).

EIMS: *m*/*z* (%) = 186 (100, M$^+$).

5-Cyclohexylmethyl-4-ethyl-1*H*-imidazole (3b)
Yield: 15% (method A), 52% (method B); mp 122–124 °C.

^{1}H NMR (DMSO-d_6): δ = 0.82–0.93 (m, 2 H, H$_{cy}$), 1.07–1.18 (m, 6 H, C*H*$_3$CH$_2$ and H$_{cy}$), 1.44–1.61 (m, 6 H, H$_{cy}$), 2.30 (d, 2 H, *J* = 7.0 Hz, C*H*$_2$Cy), 2.42 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 7.39 (s, 1 H, H-2).

^{13}C NMR (DMSO-d_6): δ = 14.69 (*C*H$_3$CH$_2$), 18.30 (CH$_3$*C*H$_2$), 25.68, 26.01, 38.08 (C$_{cy}$), 32.54 (*C*H$_2$Cy and C$_{cy}$), 127.83 (C-4), 132.54 (C-2).

EIMS: *m*/*z* (%) = 192 (32, M$^+$), 109 (100).

Anal. Calcd for C$_{12}$H$_{20}$N$_2$·0.4H$_2$O (199.51): C, 72.24; H, 10.51; N, 14.04. Found: C, 72.17; H, 10.06; N, 14.30

5-Benzyl-4-isopropyl-1*H*-imidazole (3c)
Yield: 12% (method A), 50% (method B); mp 152–154 °C.

^{1}H NMR (DMSO-d_6): δ = 1.12 [d, 6 H, *J* = 7.0 Hz, (C*H*$_3$)$_2$CH], 2.97 [hept, 1 H, *J* = 7.0 Hz, (CH$_3$)$_2$C*H*], 3.81 [s, 2 H, C*H*$_2$Ph], 7.11–7.27 (m, 5 H, Ph), 7.42 (s, 1 H, H-2).

^{13}C NMR (DMSO-*d*): δ = 22.88 [(*C*H$_3$)$_2$CH], 24.44 [(CH$_3$)$_2$*C*H], 31.34 (*C*H$_2$Ph), 125.55, 128.05, 128.11, 135.61 (C$_{arom}$), 128.24 (C-4), 132.98 (C-2), 141.05 (C-5).

EIMS: *m*/*z* (%) = 200 (76, M$^+$), 185 (100).

5-Cyclohexylmethyl-4-isopropyl-1*H*-imidazole (3d)
Yield: 20% (method A), 68% (method B); mp 120–122 °C.

^{1}H NMR (DMSO-d_6): δ = 0.82–0.93 (m, 2 H, H$_{cy}$), 1.12–1.17 [m, 8 H, (C*H*$_3$)$_2$CH and H$_{cy}$], 1.43–1.61 (m, 6 H, H$_{cy}$), 2.30 (d, 2 H, *J* = 7.2 Hz, C*H*$_2$Cy), 2.85 [hept, 1 H, *J* = 6.9 Hz, (CH$_3$)$_2$C*H*], 7.35 (s, 1 H, H-2).

^{13}C NMR (DMSO-d_6): δ = 23.11 [(*C*H$_3$)$_2$CH], 24.57 [(CH$_3$)$_2$*C*H], 25.69, 26.02, 32.57, 38.07 (C$_{cy}$), 32.49 (*C*H$_2$Cy), 132.53 (C-2).

EIMS: *m*/*z* (%) = 206 (58, M$^+$), 123 (100).

Anal. Calcd for C$_{13}$H$_{22}$N$_2$·0.25H$_2$O (210.84): C, 74.06; H, 10.76; N, 13.29. Found: C, 74.09; H, 10.55; N, 13.54.

1*H*-Imidazoles 3a–d and 1*H*-Imidazoles-2-Sulfinic Acids Ethyl Ester 4a–d, Method B; General Procedure
To a solution of each of compounds **1a**–**d** (5 mmol) in EtOH (20 mL) was added 35% H$_2$O$_2$ (1.5 mL, 15 mmol) in one portion. The mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure and H$_2$O (20 mL) was added to the residual oil. The reaction mixture was extracted with Et$_2$O (3 × 20 mL). The combined ether extracts were dried (Na$_2$SO$_4$), filtered, and evaporated in vacuo to afford the ethyl ester of imidazole-2-sulfinic acids **4a**–**d**. The H$_2$O layer was neutralized with10% aq NaHCO$_3$, extracted with EtOAc (3 × 20 mL), the EtOAc extracts were collected, dried (Na$_2$SO$_4$), filtered, and evaporated under reduced pressure. The residual material was dried to afford compounds **3a**–**d**. The yields of **3a**–**d** are given above under the products of Method A.

5-Benzyl-4-ethyl-1*H*-imidazole-2-sulfinic Acid Ethyl Ester (4a)
Yield: 0.3 g (22%); oil.

^{1}H NMR (DMSO-d_6): δ = 1.07 (t, 3 H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.18 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 2.54 (q, 2 H, *J* = 7.4 Hz, CH$_3$C*H*$_2$), 3.78 (dq, 1 H, *J* = 10.2, 7.1 Hz, OC*H*HCH$_3$), 3.88 (s, 2 H, C*H*$_2$Ph), 4.10 (dq, 1 H, *J* = 10.1, 7.1 Hz, OCH*H*CH$_3$), 7.14–7.29 (m, 5 H, Ph), 13.00 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.20 (*C*H$_3$CH$_2$), 15.21 (*C*H$_3$CH$_2$), 17.94 (br, CH$_3$*C*H$_2$), 31.06 (br, *C*H$_2$Ph), 61.31 (O*C*H$_2$CH$_3$), 125.84, 128.14, 128.19, 140.02 (C$_{arom}$), 144.61 (C-2).

EIMS: *m*/*z* (%) = 278 (38, M$^+$), 233 (100).

5-Cyclohexylmethyl-4-ethyl-1*H*-imidazole-2-sulfinic Acid Ethyl Ester (4b)
Yield: 0.23 g (16%); mp 98–100 °C.

^{1}H NMR (CDCl$_3$): δ = 0.88–0.98 (m, 2 H, H$_{cy}$), 1.11–1.32 (m, 9 H, C*H*$_3$CH$_2$, C*H*$_3$CH$_2$O and H$_{cy}$), 1.55–1.72 (m, 6 H, H$_{cy}$), 2.44 (d, 2 H, *J* = 6.8 Hz, C*H*$_2$Cy), 2.59 (q, 2 H, *J* = 7.4 Hz, CH$_3$C*H*$_2$) 3.79 (dq, 1 H, *J* = 9.8, 7.1 Hz, OC*H*HCH$_3$), 4.16 (dq, 1 H, *J* = 9.8, 7.1 Hz, OCH*H*CH$_3$), 10.70 (br s, 1 H, NH).

^{13}C NMR (CDCl$_3$): δ = 14.26 (*C*H$_3$CH$_2$), 15.32 (*C*H$_3$CH$_2$), 19.04 (br, CH$_3$*C*H$_2$), 26.12, 26.35, 38.49 (C$_{cy}$), 33.06 (*C*H$_2$Cy and C$_{cy}$), 61.97 (O*C*H$_2$CH$_3$), 143.70 (C-2).

EIMS: *m*/*z* (%) = 284 (30, M$^+$), 55 (100).

Anal. Calcd for C$_{14}$H$_{24}$N$_2$O$_2$S·0.6H$_2$O (295.23): C, 56.96; H, 8.60; N, 9.49. Found: C, 56.73; H, 8.19; N, 9.66.

5-Benzyl-4-isopropyl-1*H*-imidazole-2-sulfinic Acid Ethyl Ester (4c)
Yield: 0.15 g (10%); oil.

^{1}H NMR (DMSO-d_6): δ = 1.12–1.20 [m, 9 H, C*H*$_3$CH$_2$ and (C*H*$_3$)$_2$CH], 2.20–3.00 [m, 1 H, (CH$_3$)$_2$C*H*], 3.80 (dq, 1 H, *J* = 10.3, 7.1 Hz, OC*H*HCH$_3$), 3.90 (s, 2 H, C*H*$_2$Ph), 4.09 (dq, 1 H, *J* = 10.3, 7.1 Hz, OCH*H*CH$_3$), 7.16–7.29 (m, 5 H, Ph), 12.97 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 15.20 (*C*H$_3$CH$_2$), 22.36 [(*C*H$_3$)$_2$CH], 24.83 [(CH$_3$)$_2$*C*H], 30.59 (*C*H$_2$Ph), 61.36 (O*C*H$_2$CH$_3$), 125.83, 128.08, 128.23 (C$_{arom}$), 144.81 (C-2).

HRMS MALDI: *m*/*z* calcd for C$_{15}$H$_{21}$NaN$_2$O$_2$S (MH$^+$), 293.1323; found, 293.1317

5-Cyclohexylmethyl-4-isopropyl-1*H*-imidazole-2-sulfinic Acid Ethyl Ester (4d)
Yield: 0.2 g (13%); semisolid.

^{1}H NMR (DMSO-d_6): δ = 0.88–0.96 (m, 2 H, H$_{cy}$), 1.06–1.19 [m, 9 H, (C*H*$_3$)$_2$CH and H$_{cy}$], 1.55–1.66 (m, 6 H, H$_{cy}$), 2.39 (d, 2 H, 6.8 Hz, C*H*$_2$Cy), 2.92 [hept, 1 H, 6.9 Hz, (CH$_3$)$_2$C*H*], 3.79 (dq, 1 H, *J* = 10.3, 7.1 Hz, OC*H*HCH$_3$), 4.08 (dq, 1 H, *J* = 10.3, 7.1 Hz, OCH*H*CH$_3$).

^{13}C NMR (DMSO-d_6): δ = 15.15 (*C*H$_3$CH$_2$), 22.56 [(*C*H$_3$)$_2$CH], 24.85 [(CH$_3$)$_2$*C*H], 25.62, 25.92, 32.40, 37.92 (C$_{cy}$), 32.37 (*C*H$_2$Cy), 61.23 (O*C*H$_2$CH$_3$).

HRMS MALDI: *m*/*z* calcd for C$_{15}$H$_{27}$N$_2$O$_2$S (MH$^+$), 299.1793; found, 299.1792.

4-Cyclohexylmethyl-5-ethylimidazole-1-sulfonic Acid Dimethylamide (5) and 4-Alkyl-5-cyclohexylmethyl-imidazole-1-sulfonic Acids Dimethylamide 6a,b
To a mixture of each of the compounds **3b**,**d** (10 mmol) and Et$_3$N (1.4 mL, 10 mmol) in toluene (40 mL), dimethylsulfamoyl chloride (1 mL, 10 mmol) in toluene (10 mL) was added dropwise. The mixture was stirred at r.t. for 1 h followed by refluxing for 5 h. After cooling to r.t., H$_2$O (50 mL) was added to the reaction mixture and

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the two layers were separated. The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The residual material was chromatographed on a silica gel column with CH_2Cl_2–EtOAc (1:1) to afford compounds **5** and **6a**,**b**.

4-Cyclohexylmethyl-5-ethyl-imidazole-1-sulfonic Acid Dimethylamide (5)
Yield: 1 g (33%); mp 52–54 °C.

^{1}H NMR ($CDCl_3$): δ (ppm) = 0.88–1.00 (m, 2 H, H_{cy}), 1.08–1.31 (m, 6 H, C*H*$_3$CH$_2$ and H_{cy}), 1.67 –1.78 (m, 6 H, H_{cy}), 2.34 (d, 2 H, *J* = 6.7 Hz, C*H*$_2$Cy), 2.72 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 2.87 [s, 6 H, $(CH_3)_2$N], 7.00 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.95 (*C*H$_3$CH$_2$), 17.10 (CH$_3$*C*H$_2$), 26.22, 26.49, 33.28, 37.92 (C_{cy}), 34.60 (*C*H$_2$Cy), 37.64 [$(CH_3)_2$N], 129.05 (C-4), 136.65 (C-2), 139.47 (C-5).

EIMS: *m*/*z* (%) = 299 (13, M^+), 109 (100).

Anal. Calcd for $C_{14}H_{25}N_3O_2S·0.2H_2O$ (303.04): C, 55.49; H, 8.45; N, 13.87. Found: C, 55.66; H, 8.29; N, 13.81.

5-Cyclohexylmethyl-4-ethyl-imidazole-1-sulfonic Acid Dimethylamide (6a)
Yield: 0.75 g (25%); mp 96–98 °C.

^{1}H NMR ($CDCl_3$): δ = 0.88–0.99 (m, 2 H, H_{cy}), 1.11–1.26 (m, 6 H, C*H*$_3$CH$_2$ and H_{cy}), 1.58–1.70 (m, 6 H, H_{cy}), 2.48 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 2.55 (d, 2 H, *J* = 6.6 Hz, C*H*$_2$Cy), 2.84 [s, 6 H, $(CH_3)_2$N], 7.03 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 13.44 (*C*H$_3$CH$_2$), 20.41 (CH$_3$*C*H$_2$), 26.21, 26.36, 33.07, 37.94 (C_{cy}), 31.36 (*C*H$_2$Cy), 38.47 [$(CH_3)_2$N], 125.21 (C-4), 137.07 (C-2), 142.95 (C-5).

EIMS: *m*/*z* (%) = 299 (100, M^+).

Anal. Calcd for $C_{14}H_{25}N_3O_2S$ (299.43): C, 56.16; H, 8.42; N, 14.03. Found: C, 56.31; H, 8.43; N, 13.99.

5-Cyclohexylmethyl-4-isopropylimidazole-1-sulfonic Acid Dimethylamide (6b)
Yield: 1.72 g (55%); mp 122–124 °C.

^{1}H NMR ($CDCl_3$): δ = 0.88–1.02 (m, 2 H, H_{cy}), 1.07–1.28 [m, 9 H, $(CH_3)_2$CH and H_{cy}], 1.59–1.82 (m, 6 H, H_{cy}), 2.56 (d, 2 H, *J* = 7.0 Hz, C*H*$_2$Cy), 2.82–2.90 [m, 7 H, $(CH_3)_2$C*H* and $(CH_3)_2$N], 7.84 (s, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 22.41 [$(CH_3)_2$CH], 25.87 [$(CH_3)_2$*C*H], 26.26, 26.36, 33.07, 37.96 (C_{cy}), 31.56 (*C*H$_2$Cy), 38.36 [$(CH_3)_2$N], 124.17 (C-4), 137.31 (C-2), 146.90 (C-5).

EIMS: *m*/*z* (%) = 313 (100, M^+).

Anal. Calcd for $C_{15}H_{27}N_3O_2S$ (313.45): C, 57.48; H, 8.68; N, 13.41. Found: C, 57.72; H, 8.67; N, 12.97.

4-Cyclohexylmethyl-5-ethyl-2-hydroxymethylimida-zole-1-sulfonic Acid Dimethylamide (7) and 4-Alkyl-5-cyclohexylmethyl-2-hydroxymethylimidazole-1-sulfonic Acids Dimethylamide 8a,b
Each of the compounds **5** and **6a**,**b** (1.5 mmol) was dissolved in THF (20 mL) under nitrogen and the solution was cooled to –78 °C. *n*-BuLi (0.81 mL, 2.2 M in *n*-hexane, 1.8 mmol) was added and the mixture was stirred for 0.5 h at –78 °C. Then DMF (0.14 mL, 1.8 mmol) was added dropwise at –78 °C. The reaction mixture was allowed to reach r.t. and quenched with H_2O (5 mL). EtOH (10 mL) was added to the reaction mixture followed by addition of $NaBH_4$ (0.057g, 1.5 mmol) portion-wise. After filtration, Et_2O (30 mL) was added to the filtrate, and the two layers were separated. The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The residual material was chromatographed on a silica gel column with CH_2Cl_2–MeOH (1:1) to afford compounds **7** and **8a**,**b**.

4-Cyclohexylmethyl-5-ethyl-2-hydroxymethylimida-zole-1-sulfonic Acid Dimethylamide (7)
Yield: 0.15 g (30%); 100–102 °C.

^{1}H NMR ($CDCl_3$): δ = 0.85–0.92 (m, 2 H, H_{cy}), 1.22–1.25 (m, 6 H, C*H*$_3$CH$_2$ and H_{cy}), 1.66–1.71 (m, 6 H, H_{cy}), 2.30 (d, 2 H, *J* = 6.8 Hz, C*H*$_2$Cy), 2.70 (q, 2 H, *J* = 7.4 Hz, CH$_3$C*H*$_2$), 3.58 (br s, 1 H, OH), 4.79 (s, 2 H, C*H*$_2$OH).

^{13}C NMR ($CDCl_3$): δ = 15.04 (*C*H$_3$CH$_2$), 17.62 (CH$_3$*C*H$_2$), 26.21, 26.48, 33.28, 37.82 (C_{cy}), 34.39 (*C*H$_2$Cy), 37.45 [$(CH_3)_2$N], 59.33 (CH$_2$OH), 130.97 (C-4), 137.11 (C-2), 148.39 (C-5).

EIMS: *m*/*z* (%) = 329 (19, M^+), 139 (100).

Anal. Calcd for $C_{15}H_{27}N_3O_3S$ (329.46): C, 54.68; H, 8.26; N, 12.75. Found: C, 55.12; H, 8.31; N, 12.35.

5-Cyclohexylmethyl-4-ethyl-2-hydroxymethylimida-zole-1-sulfonic Acid Dimethylamide (8a)
Yield: 0.26 g (52%); mp 84–86 °C.

^{1}H NMR ($CDCl_3$): δ = 0.83–0.97 (m, 2 H, H_{cy}), 1.10–1.26 (m, 6 H, C*H*$_3$CH$_2$ and H_{cy}), 1.56–1.70 (m, 6 H, H_{cy}), 2.45 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 2.54 (d, 2 H, *J* = 6.9 Hz, C*H*$_2$Cy), 2.86 [s, 6 H, $(CH_3)_2$N], 3.77 (br s, 1 H, OH), 4.80 (s, 2 H, C*H*$_2$OH).

^{13}C NMR ($CDCl_3$): δ = 13.43 (*C*H$_3$CH$_2$), 20.27 (CH$_3$*C*H$_2$), 26.26, 26.38, 33.13, 37.87 (C_{cy}), 31.91 (*C*H$_2$Cy), 38.54 [$(CH_3)_2$N], 59.36 (CH$_2$OH), 127.09 (C-4), 140.59 (C-2), 148.96 (C-5).

HRMS MALDI: *m*/*z* calcd for $C_{15}H_{28}N_3O_3S$ (MH^+) 330.184, found, 330.185.

5-Cyclohexylmethyl-2-hydroxymethyl-4-isopropyl-imidazole-1-sulfonic Acid Dimethylamide (8b)
Yield: 0.25 g (48%); mp 118–120 °C.

^{1}H NMR ($CDCl_3$): δ = 0.86–0.97 (m, 2 H, H_{cy}), 1.11–1.26 [m, 9H, $(CH_3)_2$CH and H_{cy}], 1.56–1.71 (m, 6 H, H_{cy}), 2.55 (d, 2 H, *J* = 6.8 Hz, C*H*$_2$Cy), 2.78–2.85 [m, 7 H, $(CH_3)_2$C*H* and $(CH_3)_2$N], 3.79 (br s, 1 H, OH), 4.79 (s, 2 H, C*H*$_2$OH).

^{13}C NMR ($CDCl_3$): δ = 22.35 [$(CH_3)_2$CH], 25.72 [$(CH_3)_2$*C*H], 26.30, 26.38, 33.11, 37.85 (C_{cy}), 31.67 (*C*H$_2$Cy), 38.40 [$(CH_3)_2$N], 59.38 (CH$_2$OH), 126.00 (C-4), 144.45 (C-2), 149.08 (C-5).

EIMS: *m*/*z* (%) = 343 (57, M^+), 260 (100).

Anal. Calcd for $C_{16}H_{29}N_3O_3S$ (343.48): C, 55.95; H, 8.51; N, 12.23. Found: C, 55.78; H, 8.50; N, 12.11.

(5-Cyclohexylmethyl-4-alkyl-1*H*-imidazol-2-yl)methanols 9a,b
A suspension of each of the compounds **7** and **8a**,**b** (3.5 mmol) in 1.5 M HCl (30 mL) was refluxed for 5 h. The solid product formed was filtered, washed with aq $NaHCO_3$ (20 mL), Et_2O (30 mL), and dried to afford compounds **9a**,**b**.

(5-Cyclohexylmethyl-4-ethyl-1*H*-imidazol-2-yl)methanol (9a)
Yield: 70% (obtained from hydrolysis of compound **7**), 75% (obtained from hydrolysis of compound **8a**).

^{1}H NMR ($CDCl_3$): δ = 0.82–0.92 (m, 2 H, H_{cy}), 1.05–1.20 (m, 6 H, C*H*$_3$CH$_2$ and H_{cy}), 1.43–1.62 (m, 6 H, H_{cy}), 2.25 (d, 2 H, *J* = 6.8 Hz, C*H*$_2$Cy), 2.37 (q, 2 H, *J* = 7.4 Hz, CH$_3$C*H*$_2$), 4.34 (s, 2 H, C*H*$_2$OH).

^{13}C NMR ($CDCl_3$): δ = 14.80 (*C*H$_3$CH$_2$), 18.38 (CH$_3$*C*H$_2$), 26.73, 26.05, 38.11 (C_{cy}), 32.60 (*C*H$_2$Cy and C_{cy}), 56.93 (CH$_2$OH), 145.24 (C-2).

EIMS: *m*/*z* (%) = 222 (24, M^+), 139 (100).

Anal. Calcd for $C_{13}H_{22}N_2O·0.1H_2O$ (224.13): C, 69.67; H, 9.97; N, 12.50. Found: C, 69.55; H, 10.22; N, 12.51.

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(5-Cyclohexylmethyl-4-isopropyl-1*H*-imidazol-2-yl)methanol (9b)

Yield: 0.66 g (80%); mp 128–130 °C.

^{1}H NMR ($CDCl_3$): δ = 0.83–0.93 (m, 2 H, H_{cy}), 1.05–1.21 [m, 9 H, (CH_3)$_2$CH and H_{cy}], 1.43–1.63 (m, 6 H, H_{cy}), 2.27 (d, 2 H, *J* = 6.9 Hz, CH_2Cy), 2.81 [hept, 1 H, *J* = 6.8 Hz, (CH_3)$_2$C*H*], 4.35 (s, 2 H, CH_2OH].

^{13}C NMR ($CDCl_3$): δ = 23.12 [(CH_3)$_2$CH], 24.66 [(CH_3)$_2$*C*H], 25.73, 26.05, 38.07 (C_{cy}), 32.06 (CH_2Cy and C_{cy}), 56.94 (CH_2OH), 145.27 (C-2).

EIMS: *m*/*z* (%) = 236 (26, M^+), 153 (100).

Anal. Calcd for $C_{14}H_{24}N_2O$ (236.36): C, 71.14; H, 10.23; N, 11.85. Found: C, 70.94; H, 10.55, N, 11.74.

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