Synthesis of some new 2-heterosubstituted 4,5-dihydroimidazoles

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Dedicated to Professor Charles Rees on his 75th birthday
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Abstract
Several new 4,5-dihydroimidazoles (and the corresponding imidazolium salts) carrying heteroatom substituents at C-2 have been prepared from the corresponding tetrahydroimidazol-2-ones and/or -thiones.

Keywords: 4,5-Dihydroimidazole, imidazolium salt, imidazoline

Introduction
As part of a programme to prepare optically active nitrogen heterocycles,1 we have reported on the use of 4,5-dihydroimidazolium ylides 2, available from the 4,5-dihydroimidazoles (2-imidazolines) 1, in the assembly of pyrrolo[1,2-a]imidazoles (Scheme 1).2 Reductive removal of the templating atoms affords pyrrolidines.3

![Scheme 1](image)

Scheme 1. Synthesis of optically active pyrrolidines from 4,5-dihydroimidazolium ylides.

We proposed to extend this strategy to 2-heteroatom substituted 4,5-dihydroimidazoles 3 and their quaternary salts with the expectation that the corresponding cycloadducts 4 could lead to pyrrolidones on template removal (Scheme 2). Although this strategy was ultimately not fruitful,
we report here the preparation of new 2-thioalkyl, 2-alkoxy and 2-alkylamino 4,5-dihydroimidazoles 3 and of the corresponding N-alkyl-4,5-dihydroimidazolium salts.

Our first approach was to employ the chemistry of 1-benzyl-2-lithio-4,5-dihydroimidazole that we have reported,\(^4\) to generate 2-alkylthio or 2-arylthio derivatives.

![Scheme 2. Proposed synthesis of pyrrolidones (ZR\(_n\) = OR, SR, NR\(_2\)).](image)

The sulfur substituent could also act as a leaving group to access O- and N-substituted compounds. When 1-benzyl-4,5-dihydroimidazole\(^5\) was deprotonated (BuLi, THF, \(-78^\circ\)C) and reacted with diphenyl or dibutyl disulfides, the sulfur-substituted dihydroimidazoles 5\(_{a,b}\) were isolated (Scheme 3), however the major product (40\%) was 1-benzyl-tetrahydroimidazol-2-one 6\(_a\), arising presumably from adventitious hydrolysis during isolation.

![Scheme 3](image)

This prompted us to explore an alternative approach to 3 via this cyclic urea 6\(_a\) and sulfur analogue 6\(_b\), which were readily available in good yield by reaction of N-benzyl-1,2-diaminoethane with 1,1’-carbonyldimidazole and 1,1’-thiocarbonyldimidazole, respectively (Scheme 4). Attempts to O-alkylate urea 6\(_a\) using Meerwein’s salts or methyl trifluoromethanesulfonate (MeOTf) were unproductive in our hands. In contrast, thiourea 6\(_b\) was readily methylated on sulfur (MeI, heat; or MeOTf, 20\(^\circ\)C) to provide the salt 7 that was neutralised (solid K\(_2\)CO\(_3\)) to give to the first of the targets 3, the 2-methylthio compound 8 (86\%). Salt 7 also proved useful in preparation of other 2-heteroatom substituted 4,5-dihydroimidazoles. Thus treatment with sodium ethoxide (EtOH reflux, 24h) afforded the 2-ethoxy derivative 9 (66\%). The 2-amino compounds 10\(_{a,b}\) were prepared using ethylamine (THF reflux, 20h; 75\%) and pyrrolidine (reflux, 20h; 47\%), respectively; no reaction was observed with the bulky tert-butylamine or the aromatic amine aniline.
Having a secure access to 2-heteroatom-substituted 4,5-dihydroimidazoles, we next targeted the corresponding 1-benzyl-3-alkoxycarbonylmethyl-4,5-dihydroimidazolium salts as direct precursors to 4,5-dihydroimidazolium ylides. Disappointingly, heating 2-methylthio compound 8 with methyl bromoacetate (THF reflux, 5h) gave no reaction, and attempted alkylation with iodoacetonitrile or ethyl methanesulfonyloxyacetate were also fruitless. The 2-ethoxy 9 and 2-amino-4,5-dihydroimidazoles 10 behaved similarly. We therefore decided to reverse the sequence of incorporation of C-2 and C-3 substituents. The cyclic urea 6a was converted into the N-methoxycarbonylmethyl compound 11a by deprotonation with sec-BuLi (THF, –78°C) and reaction with methyl bromoacetate (THF reflux, 24h; 41%) (Scheme 4); other bases proved less effective. Neither this method, nor Mitsunobu conditions using ethyl glycolates, were successful in the analogous reactions of thiourea 6b, and direct treatment of 6b with methyl bromoacetate (THF reflux, 18h) afforded the S-alkylation product 12 (87%). The N-alkylated thiourea 11b was however accessed by thionation of urea 11a with Lawesson’s reagent (o-xylene reflux, 26h; 66%).

![Scheme 4](image_url)

In order to generate 4,5-dihydroimidazolium ylides from urea 11a and thiourea 11b, O- or S-alkylation, respectively, was required. S-Methylation of 11b was accomplished with MeOTf to afford a salt 13 which displayed the expected NMR spectral characteristics but was not completely characterised. NMR spectroscopic evidence was likewise obtained for salts 14a-c prepared in an NMR tube from urea 11a using triethyloxonium tetrafluoroborate,
trifluoromethanesulfonic anhydride and tert-butyl-dimethylsilyl trifluoromethanesulfonate, respectively. Downfield shifts of product peaks were observed relative to the urea, although these putative salts proved too hygroscopic for further analysis. In any event, one-pot attempts by our usual protocol to induce formation of salts 13 or 14, deprotonation to an ylide and cycloaddition were unsuccessful. The major isolated product in each case was urea 11a, presumably from quaternary salt hydrolysis.

Figure 1. 4,5-Dihydroimidazolium salts observed spectroscopically.

We prepared two alternative series of 1,3-disubstituted tetrahydroimidazolin-2-ones and 2-thiones as potential ylide precursors. In the first of these, cyclic urea 6a was N-silylmethylated to give 15a (NaH, DMSO, Me3SiCH2Cl or Me3SiCH2I; 45%) (Scheme 5), with a view ultimately to ylide generation by desilylation. 1-Benzyl-3-methyltetrahydroimidazol-2-one 16 was isolated as a by-product (27%). The thiourea 15b was prepared from 15a by thionation (Lawesson’s reagent, o-xylene reflux; 69%). As above, O-alkylation of 15a was attempted (NMR tube) with MeOTf or triethyloxonium tetrafluoroborate but proceeded only to partial conversion after several hours. Attempted one-pot alkylation, desilylation (CsF) and cycloaddition was unsurprisingly unsuccessful with 15a. With 15b, although salt 17 could be observed (NMR) using MeOTf as alkylating agent, the one-pot protocol returned unchanged thiourea 15b and urea 15a, representing presumably incomplete S-alkylation and hydrolysis of S-alkyl salt 17.

Scheme 5
The second alternative series of (thio)ureas comprised the 1,3-dibenzyl compounds 18a,b, readily available from commercial N,N'-dibenzyldiamino-1,2-diaminoethane and carbonyl or thiocarbonyldiimidazole, respectively (18a 97%; 18b 98%) (Scheme 6). S-Methylation of 18b (MeOTf, CH₂Cl₂, 20°C) afforded salt 19 in quantitative yield. This salt provided access to 2-imino compound 20 (MeNH₂, THF reflux 18h; 40%). The salt 21 was observed spectroscopically from 19 and pyrrolidine, as were salts 22a-c from reaction of urea 18a with trifluoromethanesulfonic anhydride, trimethylsilyl trifluoromethane-sulfonate or tert-butyldimethylsilyl trifluoromethanesulfonate, respectively. To test for benzylic deprotonation in this series, (thio)ureas 18a,b were treated with base (sec-BuLi, THF, -78°C) and quenched with CF₃CO₂D, when clean mono-deuteration was observed (PhCH₂ signal, 4H at δ 4.41 and 4.92 respectively, converted to two singlets 0.03 ppm apart, integrating as 2H and 1H). Similar treatment of the salt 22c afforded mono-deuteration. However, when the salts 19, 21 and 22a-c were subjected to the one-pot deprotonation-cycloaddition protocol with methylacrylate, no cycloadducts were observed.

![Scheme 6](image-url)

**Figure 2.** 4,5-Dihydroimidazolium salts observed spectroscopically.

These studies, whilst not to date affording 1,3-dipolar cycloaddition, have generated some new 2-heteroatom substituted 4,5-dihydroimidazoles via cyclic ureas, and explored generation of the corresponding imidazolium salts.
Experimental Section

General Procedures. Proton (1H) and carbon (13C) NMR spectra were recorded in CDCl₃ using either a JEOL EX400 (400 and 100MHz, respectively) or a JEOL LA300 spectrometer (300 and 75MHz, respectively). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as the internal standard. Multiplicities are given as: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, sext-sexet, m-multiplet, br-broad signal. Coupling constants (J) are expressed in Hz. Infrared spectra were recorded using a Perkin-Elmer 1710 Fourier Transform infrared spectrophotometer. Low resolution mass spectra were recorded using a VG Micromass VG-250 mass spectrometer by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) methods, the latter employing a thioglycerol matrix in both positive and negative ion modes. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (University of Wales, Swansea, UK). Elemental analyses were performed by MEDAC Ltd, Brunel Science Centre, Surrey, TW20 0JZ, UK. X-Ray crystallography was performed by the EPSRC X-Ray Crystallographic Service (University of Southampton, UK). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was carried out using Fluka Silica Gel 60 (220-440mesh) (Brockmann 2-3). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV 254 plates on a plastic backing and visualised by ultraviolet light or aqueous potassium permanganate spray (KMnO₄:K₂CO₃:water, 6:1:100, w/w/v).

All chemicals were purified by distillation or recrystallisation where appropriate. THF, THP, diethyl ether, toluene, ethanol and glyme were dried over sodium or potassium and distilled. DCM and DMSO were dried over sodium or calcium hydride and distilled. Anhydrous reactions were carried out using flame dried glassware with all transfers performed using oven-dried syringes and needles.

1-Benzyltetrahydroimidazol-2-one (6a). To N-benzyl-1,2-diaminoethane (5.00 g; 33.0 mmol) in dry THF (200 ml) under nitrogen was added a solution of 1,1′-carbonyldiimidazole (6.48 g; 40.0 mmol) in dry THF (25 ml). The resulting solution was stirred at RT for 18 h. The solvent was removed under reduced pressure and the mixture was washed with dilute hydrochloric acid (2M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄) and the solvent removed under reduced pressure to afford the title compound 6a as a white crystalline solid (5.79 g; 99%): m.p. 124-127°C (lit., 8 127°C) (Found: (EI): M⁺ 176.0941; C₁₀H₁₂N₂O requires M⁺ 176.0949); νmax(nujol)/cm⁻¹ 1601, 1496, 1467, 1301 and 1116; δH (400 MHz) 3.38 and 3.42 (each m, 2H, NCH₂CH₂N), 4.40 (s, 2H, C₆H₂Ph), 7.29 (m, 5H, Ar-H); δC (100 MHz) 38.2 (CH₂Ph) 44.5 and 47.7 (CH₂N), 127.5, 128.1 and 128.6 (Ar-CH) 136.9 (Ar-C), 162.8 (CO); m/z (EI) 176 (M⁺, 100%), 161 (2), 147 (35), 132 (7), 104 (43), 99 (28), 91 (91), 85 (27), 77(9), 65 (21), 56 (8).
1-Benzyltetrahydroimidazol-2-thione (6b). Prepared according to the method used to synthesize 6a, using N-benzyl-1,2-diaminoethane (0.50 g; 3.30 mmol) in dry THF (33 ml) and 1,1′-thiocarbonyl-diimidazole (0.71 g; 3.99 mmol) in dry THF (5 ml) to afford the title compound 6b as a white crystalline solid (0.60 g; 94%): m.p. 181-182°C (lit.,9 177-182°C) (Found: (FAB): M⁺ 192.0711; C₁₀H₁₂N₂S requires M⁺ 192.0721; υ max(nujol)/cm⁻¹ 3401, 2924, 1556, 1377, and 722; δH (400 MHz) 3.60 (s, 4H, NCH₂CH₂N) 4.84 (s, 2H, C₆H₂Ph), 7.38 (m, 5H, Ar-H); δC (100 MHz) 41.3 (C₆H₂Ph) 48.0 and 51.0 (CH₂N), 127.8, 128.2 and 128.7 (Ar-CH), 135.1 (Ar-C), 183.2 (CS); m/z (EI) 192 (M⁺, 55%), 176 (2), 131 (10), 104 (20), 91 (100), 89 (7), 77 (13), 68 (37), 65 (32), 56 (12).

1-Benzyl-2-methylthio-4,5-dihydroimidazole (8). Iodomethane (32.0 ml; 50.0 mmol) was added to 1-benzyltetrahydroimidazol-2-thione 6b (2.03 g; 10 mmol) and the mixture heated at reflux for 16 h under nitrogen. After allowing the mixture to cool to RT the excess MeI was removed under reduced pressure and the residue evaporated twice from dry methanol (2 × 10 ml) to afford the imidazolium salt 7 as a yellow solid (1.89 g, 87%): m.p. 102-105°C; δH (400 MHz) 2.68 (s, 3H, SCH₃), 4.04 and 4.10 (each t, 2H, J = 9.2, NCH₂CH₂N), 4.60 (s, 2H, C₆H₂Ph), 7.33 (m, 5H, Ar-H); δC (100 MHz) 16.2 (SCH₃), 51.9 (C₆H₂Ph), 53.3 and 53.8 (CH₂N), 127.6, 128.3 and 128.7 (Ar-CH), 137.4 (Ar-C), 164.1 (NCS). The salt 7 (1.88 g; 5.6 mmol) in dichloromethane (50 ml) was treated with excess K₂CO₃ (7.7 g) and the resulting solution stirred at RT for 1 h. The solution was filtered, extracted with dichloromethane (2 × 50 ml) and the combined organic phases dried (MgSO₄). The solvent was removed under reduced pressure to afford the title compound 8 as a yellow solid (1.61 g, 86%) (Found: (FAB): M⁺ 206.0875; C₁₁H₁₄N₂S requires M⁺ 206.0877): m.p. 95-98°C; υ max(nujol)/cm⁻¹ 3128, 1587, 1563, 1497, 738 and 723; δH (400 MHz) 2.68 (s, 3H, SCH₃), 3.83 and 3.98 (each t, 2H, J = 9.2, NCH₂CH₂N), 4.37 (s, 2H, C₆H₂Ph), 7.28 (m, 5H, Ar-H); δC (100 MHz) 14.6 (CH₃), 38.02 (C₆H₂Ph), 48.32 and 49.75 (CH₂N), 65.11 (OCH₂), 127.8, 128.2 and 128.8 (Ar-CH), 136.2 (Ar-C), 163.8 (NCS); m/z (EI) 206 (M⁺, 18%), 191 (17), 116 (5), 91 (34), 28 (100).

1-Benzyl-2-ethoxy-4,5-dihydroimidazole (9). A freshly prepared solution of NaOEt (0.38 g; 5.7 mmol) in EtOH (20 ml) was added to 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide 7 (0.46 g; 2.3 mmol) and the resulting solution heated at reflux for 24 h. Water (10 ml) was added and the solution extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound 9 as a white solid (0.30 g; 66%): m.p. 162-165°C (Found: (FAB): M⁺ 204.1264; C₁₂H₁₆N₂O requires M⁺ 204.1262); δH (400 MHz) 1.20 (t, 3H, J = 5.2, OCH₂CH₃) 3.15 and 3.32 (each t, 2H, J = 6.6, NCH₂CH₂N), 4.14 (s, 2H, CH₂Ph), 4.19 (q, 2H, J = 5.2, OCH₂CH₂), 7.14 (m, 5H, Ar-H); δC (100 MHz) 14.62 (CH₃), 38.02 (CH₂Ph), 48.32 and 49.75 (CH₂N), 65.11 (OCH₂), 127.3, 128.1 and 128.6 (Ar-CH), 137.6 (Ar-C), 164.0 (NCO); m/z (EI) 204 (M⁺, 18%), 176 (71), 159 (4), 91 (100), 77 (5), 85 (24), 65 (19), 56 (11).

1-Benzyl-2-ethylamino-4,5-dihydroimidazole (10a). Ethylamine in THF (2M; 1.57 ml, 3.15 mmol) was added to 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide 7 (0.45 g, 2.1 mmol) in dry THF (20 ml) heated at reflux, and the resulting solution heated at reflux for a
further 20 h. The cooled solution was washed with aq. NaOH (0.1 M; 50 ml) and extracted with diethyl ether (2 × 50 ml). The organic phase was dried (MgSO₄), filtered and the remaining solvent evaporated under reduced pressure. The residue was then purified by silica gel column chromatography using 2-propylamine/chloroform (1:99 v/v) as eluant to yield the title compound 10a as a yellow gum (0.40 g, 75%) (Found: (EI): M⁺ 204.1425; C₁₂H₁₇N₃ requires M⁺ 204.1422): \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3320, 2980, 1440, 1265; \( \delta_{\text{H}} \) (400 MHz) 1.40 (t, 3H, \( J = 5.7 \), NHCH₂C₃H₃), 3.62 (m, 4H, NCH₂C₃H₂N and NHC₃H₂CH₃), 3.76 (t, 2H, \( J = 6.9 \), NCH₂CH₂N), 4.79 (s, 2H, CH₂Ph), 7.38 (m, 5H, Ar-H); \( \delta_{\text{C}} \) (100 MHz) 15.02 (CH₃) 39.27 (C₆H₂CH₃), 47.42 and 49.83 (CH₂N), 128.3, 128.6 and 129.1 (Ar-CH), 133.5 (Ar-C), 157.5 (NCN).

1-Benzyl-2-(pyrrolidin-1yl)-4,5-dihydroimidazole (10b). Pyrrolidine (0.20 ml; 2.0 mmol) was added to 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide 7 (0.42 g; 2.0 mmol) in dry THF (20 ml) heated at reflux, and the solution heated at reflux for a further 20 h. The solution was allowed to cool to RT, washed with aq. NaOH (0.1 M; 2 × 10 ml) and extracted with diethyl ether (2 × 50 ml). The combined organic layers were washed with water and the water layers extracted with diethyl ether (2 × 50 ml). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 2-propylamine/chloroform (1:99 v/v) as eluant to afford the title compound 10b as a yellow liquid (0.22 g; 47%) (Found: (EI): M⁺ 229.1566; C₁₄H₁₉N₃ requires M⁺ 229.1578): \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 2984, 1487, 1226; \( \delta_{\text{H}} \) (400 MHz) 1.89 (m, 4H, NCH₂C₃H₂C₃H₂CH₂N), 3.40 (m, 2H, NCH₂C₃H₂N), 3.42 (m, 4H, NCH₂CH₂CH₂CH₃), 3.72 (t, 2H, \( J = 6.8 \), NCH₂CH₂N), 4.34 (s, 2H, CH₂Ph), 7.28 (m, 5H, Ar-H); \( \delta_{\text{C}} \) (100 MHz) 25.5 (NCH₂C₃H₂), 49.4 (CH₂N), 50.6 (C₆H₂Ph), 52.9 and 54.2 (CH₂N), 126.9, 127.1 and 128.6 (Ar-CH), 138.5 (Ar-C), 164.6 (NCN); \( m/z \) (EI) 229 (M⁺, 54%), 200 (41), 186 (36), 159 (61), 138 (22), 125 (37), 110 (23), 91 (100), 82 (36), 70 (53), 65 (30), 55 (55), 41 (28), 28 (37).

1-Benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (11a). To 1-benzyltetrahydroimidazol-2-one 6a (1.03 g; 5.85 mmol) in dry THF (25 ml) under nitrogen at −78°C was added dropwise a solution of sec-BuLi (2.5M in hexanes; 7.02 mmol). The mixture was left at −78°C for 10 min and methyl bromoacetate (5.40 ml; 7.02 mmol) was then added dropwise. The mixture was heated at reflux for 24 h and then allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate/hexane (4:6 v/v) as eluant to afford the title compound 11a as colourless oil (0.60 g; 41%) (Found: (EI): M⁺ 248.1157; C₁₃H₁₆N₂O₃ requires M⁺ 248.1161): \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 2952, 2872, 1748, 1700, 1400, 1495, 1449, 1361, 1264, 1214, 986, 937, 760, 703; \( \delta_{\text{H}} \) (300 MHz) 3.25 and 3.44 (each t, 2H, \( J = 10.6 \), NCH₂CH₂N), 3.75 (s, 3H, CO₂CH₃), 4.03 (s, 2H, CH₂CO₂CH₃), 4.40 (s, 2H, CH₂Ph), 7.33 (m, 5H, Ar-H); \( \delta_{\text{C}} \) (75 MHz) 42.0 (CH₂), 43.0 (CH₃), 45.6 (CH₂), 48.2 and 52.0 (CH₂N), 127.4, 128.1 and 128.6 (Ar-CH), 137.0 (Ar-C), 163.0 (NCO), 170.1 (CO); \( m/z \) (EI) 248 (M⁺, 12%), 189 (22), 175 (5), 92 (8), 91 (100), 65 (9), 42 (9).

1-Benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione (11b). To 1-benzyl-3-methoxy-carbonylmethyltetrahydroimidazol-2-one 11a (0.20 g; 0.75 mmol) in dry ortho-xylene (30 ml) was added portionwise Lawesson’s Reagent ([2,4-bis(4-methoxyphenyl)]-1,3-dithia-2,4-
diphosphetane-2,4-disulfide) (0.30 g; 0.75 mmol). The mixture heated at reflux for 26 h after which time it was allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate/hexane (4:6 v/v) as eluant to yield the title compound 11b as yellow gum (0.14 g; 66%) (Found: (EI): M+ 264.0931; C₁₃H₁₆N₂O₂S requires M+ 264.0932): ν_max(film)/cm⁻¹ 2950, 2874, 1742, 1404, 1497, 1449, 1266, 1211, 983, 762; δ_H (300 MHz) 3.45 and 3.64 (each t, 2H, J = 10.7, NCH₂CH₂N), 3.77 (s, 3H, CO₂C₃H₃), 4.44 (s, 2H, CH₂CO₂CH₃), 4.91 (s, 2H, CH₂Ph), 7.35 (m, 5H, Ar-H); δ_C (75 MHz) 45.6 (CH₂), 46.4 (CH₃), 48.8 (CH₂), 51.8 and 52.2 (CH₂N), 127.7, 128.1 and 128.7 (Ar-CH), 138.2 (Ar-C), 170.0 (CO), 183.6 (NCS); m/z (EI) 264 (M+; 40%), 205 (22), 191 (8), 141 (10), 102 (8), 91 (100), 72 (16), 65 (14), 42 (13), 28 (27).

1-Benzyl-2-methoxycarbonylmethylthio-4,5-dihydroimidazole (12). To 1-benzyltetrahydroimidazol-2-thione 6b (0.30 g; 1.56 mmol) in dry THF (25 ml) under nitrogen was added methyl bromoacetate (0.13 ml; 1.87 mmol) and the resulting solution was heated at reflux for 18 h and then allowed to cool to RT. The solvent was evaporated under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate/hexane (45:55 v/v) as eluant to afford the title compound 12 as a white solid (0.36 g; 87%): m.p. 111-112°C (Found: (EI) MH+ 265.1014; C₁₃H₁₆N₂O₂S requires MH+ 265.1010); ν_max(nujol)/cm⁻¹ 2952, 2865, 1740, 1410, 1264; δ_H (300 MHz) 3.74 (s, 3H, CO₂C₃H₃), 3.81 and 3.94 (each m, 2H, NCH₂CH₂N), 4.59 (s, 2H, SCH₂CO₂CH₃), 4.70 (s, 2H, CH₂Ph), 7.32 (m, 5H, Ar-H); δ_C (75 MHz) 35.6 (CH₂), 44.0 (CO₂C₃H₃), 49.6 (SCH₂), 51.3 and 53.6 (CH₂N), 128.0, 128.8 and 129.3 (Ar-CH), 132.3 (Ar-C), 168.4 (CO); m/z (EI) 265 (MH+; 44%), 192 (100), 159 (10), 104 (18), 91 (50).

1-Benzyl-3-methoxycarbonylmethyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate (13). To 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione 11b (0.30 g; 1.10 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere was added neat MeOTf (0.15 ml; 1.36 mmol) and the solution allowed to stir at RT for 1 h. The solvent was removed under reduced pressure to yield the title compound 13 as a yellow gum that was partially characterised (0.46 g; 97%); δ_H (300 MHz) 2.78 (s, 3H, SMe), 3.75 (m, 5H, Ar-H); δ_C (75 MHz) 17.2 (SMe), 24.4 (CO₂C₃H₃), 49.6 (SCH₂), 53.1 and 53.6 (CH₂N), 127.8, 128.4 and 128.8 (Ar-CH), 140.2 (Ar-C), 171.7 (CO), 185.1 (NCS).

1-Benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one (15a). To a suspension of NaH (0.19 g; 8.29 mmol) in dry DMSO (25 ml) was added dropwise a solution of 1-benzyl-4,5-dihydroimidazol-2-one 6a (1.46 g; 8.29 mmol) in dry DMSO (25 ml) at RT. The mixture was stirred for 30 min and then chloromethyltrimethylsilane (2.24 ml; 12.43 mmol) was added. The resulting mixture was stirred at RT for 10 h, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane (4:6 v/v) as eluant to afford the title compound 15a as colourless oil (0.99 g; 45%) (Found: (EI): M+ 262.1503; C₁₄H₂₂N₂O₃Si requires M+ 262.1501): ν_max(film)/cm⁻¹ 3030, 2952, 2860, 1696, 1444, 1359, 1251, 856, 756; δ_H (300 MHz) 0.31 (s, 9H, Si(CH₃)₃), 2.54 (s, 2H, SMe), 3.25 and 3.41 (each m, 2H, NCH₂CH₂N), 4.51 (s, 2H, CH₂Ph), 7.36 (m, 5H, Ar-H);
δ_C (75 MHz) –1.6 (SiCH₃), 35.4 and 42.5 (CH₂), 45.5 and 48.7 (CH₂N), 127.2, 128.1 and 128.5 (Ar-CH), 137.5 (Ar-C), 161.8 (NCO); m/z (EI) 262 (M⁺, 12%), 248 (5), 247 (18), 189 (4), 171 (8), 155 (7), 100 (9), 91 (100), 73 (77), 65 (16), 45 (22), 43 (13). Also isolated was 1-benzyl-3-methyl-tetrahydroimidazol-2-one 16 as a colourless oil (0.44 g; 27%) (Found: (EI) M⁺ 190.1107; C₁₁H₁₄N₂O requires M⁺ 190.1106); δ_H (300 MHz) 2.82 (s, 3H, CH₃), 3.13 and 3.18 (each m, 2H, NCH₂CH₂N), 4.37 (s, 2H, CH₂Ph); δ_C (75 MHz) 31.4 (CH₃), 42.2 (CH₂Ph), 44.9 and 48.7 (CH₂N), 127.4, 127.7 and 128.5 (Ar-CH), 137.3 (Ar-C), 161.5 (NCO); m/z (EI) 190 (M⁺, 30%), 161 (6), 113 (13), 99 (34), 92 (9), 91 (100), 89 (11), 77 (23), 65 (34), 56 (18), 51 (16), 43 (13), 42 (44), 39 (15).

1-Benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-thione (15b). To 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one 15a (0.86g; 3.28 mmol) in dry ortho-xylene (30 ml) was added portionwise Lawesson’s reagent (1.32g; 3.28 mmol). The mixture was heated at reflux for 26 h after which time it was allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using ethyl acetate/hexane (25:75 v/v) as eluant to afford the title compound 15b as a yellow gum (0.63 g; 69%) (Found: (EI): M⁺ 278.1287; C₁₄H₂₂N₂SSi requires M⁺ 278.1273): ν_max(film)/cm⁻¹ 3030, 2938, 1696, 1498, 1404, 1252, 1056, 760, 702; δ_H (300 MHz) 0.20 (s, 9H, Si(CH₃)₃), 3.12 (s, 2H, CH₂Si), 3.21 and 3.25 (each m, 2H, NCH₂CH₂N), 4.92 (s, 2H, CH₂Ph), 7.32 (m, 5H, Ar-H); δ_C (75 MHz) –1.4 (SiCH₃), 39.3 and 45.3 (CH₂), 48.5 and 52.1 (CH₂N), 127.5, 128.3 and 128.6 (Ar-CH), 136.8 (Ar-C), 182.9 (NCS); m/z (EI) 278 (M⁺, 10%), 264 (5), 263 (21), 92 (8), 91 (100), 73 (69), 65 (20), 45 (23).

1-Benzyl-3-trimethylsilylmethyl-2-methylthio-4,5-tetrahydroimidazolium trifluoromethane-sulfonate (17). To 1-benzyl-3-trimethylsilylmethyl-4,5-tetrahydroimidazol-2-thione 15b (0.10 g; 0.36 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere was added MeOTf (0.02 ml; 0.43 mmol) and the solution allowed to stir at RT for 1 h. The solvent was removed under reduced pressure to yield the title compound as a yellow gum that was partially characterised (0.15 g; 94%): δ_H (300 MHz) 2.49 (s, 3H, SCH₃), 3.14 (s, 2H, CH₂Si), 3.72 and 3.76 (each m, 2H, NCH₂CH₂N), 4.64 (s, 2H, PhCH₂), 7.24 (m, 5H, Ar-H); δ_C (75 MHz) –1.1 (SiCH₃), 17.3 (SCH₃), 44.2 and 49.1 (CH₂), 54.2 and 55.6 (CH₂N), 127.4, 128.3 and 128.6 (Ar-CH), 137.7 (Ar-C).

1,3-Dibenzyltetrahydroimidazol-2-one (18a). To commercial N,N′-dibenzyl-1,2-diaminoethane (0.40 g; 1.67 mmol) in dry THF (20 ml) under nitrogen was added 1,1′-carbonyldiimidazole (0.38 g; 2.35 mmol) in dry THF (10 ml). The resulting solution was stirred at RT for 18 h before the solvent was evaporated under reduced pressure. The residue was washed withaq. HCl (2M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄), filtered and the solvent evaporated under reduced pressure to afford the title compound 18a as a white solid (0.41 g; 97%): m.p. 90-91°C (lit., 1093-94°C) (Found: (EI): M⁺ 266.1414; C₁₂H₁₈N₂O requires M⁺ 266.1419); ν_max(nujol)/cm⁻¹ 2927, 2855, 1689, 1494, 1455, 1365, 1257, 711; δ_H (300 MHz) 3.16 (s, 4H, NCH₂CH₂N), 4.41 (s, 4H, 2 × CH₂Ph), 7.32 (m, 10H, Ar-H); δ_C (75 MHz) 42.2 (PhCH₂), 48.6 (NCH₂), 127.5, 128.3 and
128.6 (Ar-CH), 137.4 (Ar-C), 161.1 (NCO); m/z (EI) 266 (M⁺, 73%), 189 (4), 175 (71), 132 (9), 118 (6), 105 (8), 91 (100), 65 (15).

1,3-Dibenzyltetrahydroimidazol-2-thione (18b). Prepared according to the method used to synthesize 18a, using N,N'-dibenzyl-1,2-diaminoethane (0.40 g; 1.67 mmol) and 1,1'-thiocarbonyldiimidazole (0.38 g; 2.13 mmol) to afford the title compound 18b as a yellow solid (0.44 g; 98%): m.p. 87-92 °C (lit., 11 90 °C) (Found: (EI): M⁺ 282.1188; C17H18N2S requires M⁺ 282.1191); νmax(nujol)/cm⁻¹ 2927, 2855, 1494, 1462, 1378, 1359, 1334, 1268, 1240, 731; δH (400 MHz) 3.40 (s, 4H, NCH₂CH₂N) 4.92 (s, 4H, 2 × CΗ₂Ph), 7.38 (m, 10H, Ar-H); δC (100 MHz) 45.7 (PhCH), 52.1 (NCH₂), 128.0, 128.5 and 129.0 (Ar-CH) 136.7 (Ar-C), 184.8 (NCS); m/z (EI) 282 (M⁺, 20%), 191 (30), 105 (9), 91 (100), 65 (15), 56 (5).

1,3-Dibenzyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate (19). Via a syringe was added dropwise MeOTf (0.09 ml; 0.85 mmol) to 1,3-dibenzyltetrahydroimidazol-2-thione 18b (0.20 g; 0.71 mmol) in dry dichloromethane (10 ml). The solution was stirred at RT for 1 h and the solvent removed under reduced pressure to afford the title compound 19 as a yellow oil (0.32 g; 100%) (Found: (ES, M–CF3SO3): M⁺ 297.1422; C18H21F3N2O3S2 requires (M–CF3SO3)⁺ 297.1425): νmax(film)/cm⁻¹ 3034, 2944, 1591, 1574, 1499, 1455, 1357, 1262 (br), 1225 (br), 1157 (br), 1031; δH (300 MHz) 2.86 (s, 3H, SCH₃), 3.90 (s, 4H, NCH₂CH₂N), 4.92 (s, 4H, 2 × CΗ₂Ph), 7.29 (m, 6H, Ar-H), 7.37 (m, 4H, Ar-H); δC (75 MHz) 16.5 (SCH₃), 47.8 (CH₂Ph), 53.3 (NCH₂), 127.6, 127.9 and 128.5 (Ar-C), 132.4 (Ar-C), 167.2 (NCS).

1,3-Dibenzyl-2-methyliminotetrahydroimidazole (20). 2-Methylthio-4,5-dihydroimidazolium salt 19 was prepared as above from MeOTf (0.13 ml; 1.10 mmol) and 1,3-dibenzyltetrahydroimidazol-2-thione 18b (0.26 g; 0.92 mmol) and after stirring at RT for 1 h methylamine (2M solution in THF; 0.69 ml; 1.38 mmol) was added and the resulting solution heated at reflux for 18 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with 2-propylamine/chloroform (2:98 v/v) to afford the title compound 20 as a yellow gum (0.10 g; 40%) (Found: (EI): MH⁺ 280.1738; C₁₇H₂₁N₃ requires MH⁺ 280.1735); δH (300 MHz) 3.01 (s, 3H, NCH₃), 3.44 (s, 4H, NCH₂CH₂N), 4.53 (s, 4H, 2 × CΗ₂Ph), 7.26 (m, 6H, Ar-H), 7.30 (m, 4H, Ar-H); δC (75 MHz) 46.7 (CH₂Ph), 50.7 (NCH₃), 127.5, 128.4 and 129.1 (Ar-CH), 133.8 (Ar-C), 158.5 (NCN); m/z (EI) 279 (M⁺, 24%), 250 (10), 207 (16), 125 (19), 111 (35), 97 (58), 91 (23), 83 (57), 69 (77), 57 (100), 49 (27), 43 (76), 39 (15), 29 (26).

1,3-Dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolinium trifluoromethane sulfonate (21). 2-Methylthio-4,5-dihydroimidazolium salt 19 was prepared as above from MeOTf (0.12 ml; 1.10 mmol) and 1,3-dibenzyltetrahydroimidazol-2-thione 18b (0.26 g; 0.92 mmol). After stirring at RT for 1 h the solvent was removed under reduced pressure, dry THF (25 ml) and pyrrolidine (0.09 ml; 1.0 mmol) were added to the residue under nitrogen and the solution was heated at reflux for 26 h. The solvent was removed under reduced pressure to afford the title compound 21 as a brown oil that was partially characterised (0.32 g; 77%): δH (300 MHz) 1.86 (t, 4H, J = 6.6, NCH₂CH₂CH₂CH₂N), 3.61 (t, 4H, J = 6.6, NCH₂CH₂CH₂CH₂N), 3.84 (s, 4H,
NCH₂CH₂N), 4.76 (s, 4H, 2 × CH₂Ph), 7.26 (m, 6H, Ar-H), 7.39 (m, 4H, Ar-H); δC (75 MHz)
25.5, 49.4, 50.8 and 53.4 (CH₂), 126.3, 128.2 and 129.3 (Ar-CH), 134.8 (Ar-C), 162.4 (NCN).

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References

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