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Coenzyme-inspired chemistry 1: the C-2 alkylation of 4,5-dihydroimidazoles

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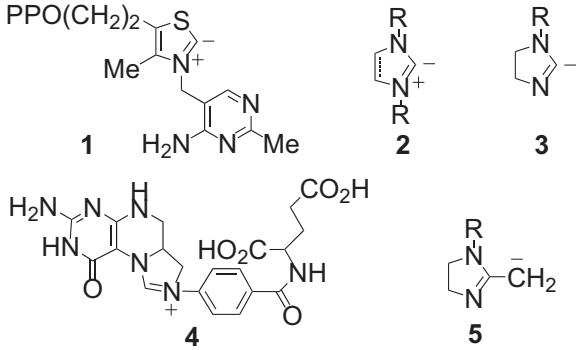
ABSTRACT

Alkylation of 4,5-dihydroimidazoles at C-2 is accomplished using a double umpolung of the reactivity of that position, via sulfenylation of a nucleophilic C-2 lithio-species and substitution using an alkyl nucleophile. Arylation via unexpected sulfide contraction from the arylsulfenylation products has also been demonstrated. Taken with dihydroimidazole cleavage protocols, this constitutes a tetrahydrofolate-inspired C1-transfer protocol.

1. Introduction

The use of C-2 'azolium' ylides derived from N-heterocycles has been of interest for many years, since the discovery by Breslow in 1957 of the involvement of a thiazolium C-2 ylide **1** in the mechanism of action of thiamine; the role of a carbene resonance form in the 'ylide' stability was also soon recognised.[1] Work by Wanzlick and others around 1960 investigated similar properties in the imidazolium system **2**, which culminated in the isolation by Arduengo in 1991 of a stable imidazolium-based carbene.[2] This interest has blossomed in recent years through the application of related ylides as N-heterocyclic carbenes (NHCs), as ligands for metals, for example, in metathesis catalysts,[3] and in organocatalysis via analogues of the Breslow intermediate in the thiamine mechanism, to provide, for example, carbonyl anions and homoenolate anions.[4]

As part of our long-standing interest in the chemistry of 4,5-dihydroimidazole (2-imidazoline),[5] we have been concerned with the C-2 anion **3** derived from this heterocycle, rather than the ylide/carbene **2**. This attracted our interest as a mimic of the tetrahydrofolate (FH4) coenzyme N^5,N^{10}-methenyl-tetrahydrofolate **4** (5,10-CH=FH4), which mediates transfer of the C-2 carbon atom of the dihydroimidazolium ring at the carboxyl oxidation level.[6] Other members of FH4 coenzyme family mediate the transfer of single carbons at the carbonyl and alcohol oxidation levels. The transfer from 5,10-CH=FH4 uses C-2 of the dihydroimidazole sub-unit as an electrophile, and we have exploited this polarity in methods using simple dihydroimidazoles for transfer at the carboxyl and carbonyl oxidation levels.[7] We were interested to reverse this reactivity in an umpolung and employ C-2 of a simple dihydroimidazole as a nucleophile, as an extension of our work with laterally metallated dihydroimidazole nucleophiles **5**[8] and intrigued by the relationship of a C-2 anion **3** to the ylide reactivity of NHCs.



We report here details of our investigation of a direct deprotonation–alkylation approach using alkyl electrophiles, which was only partially successful, a successful implementation of the C-2 nucleophile strategy by a sulfenylation–alkylation sequence using

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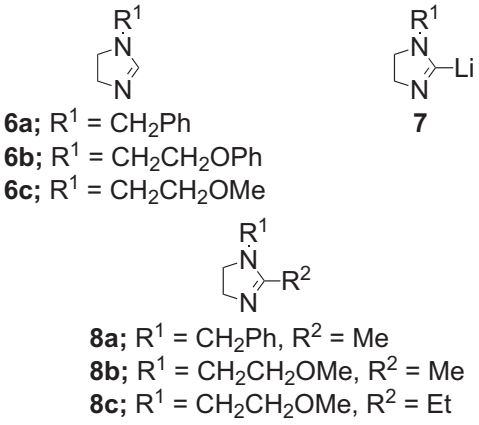
alkyl nucleophiles rather than electrophiles, and C-2 arylation by an unexpected sulfide contraction.[9] These elaborations at C-2 of a dihydroimidazole, taken with the cleavage of the ring by hydrolysis, complete a C1-transfer at the carboxylate oxidation level inspired by 5,10-CH=FH4; we have also reported a cleavage sequence leading to ketones.[7] The exploration of higher oxidation level electrophiles, using dihydroimidazolium ylides as leaving groups, will be reported separately.

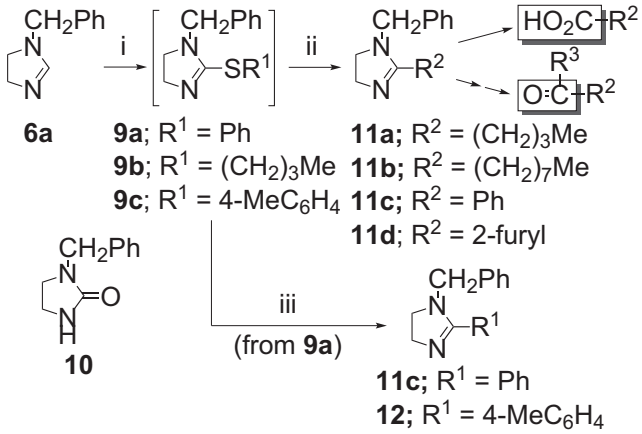
2. Results and discussion

As substrates we prepared 1-benzyl-4,5-dihydroimidazole **6a** (from *N*-benzyl-1,2-diaminoethane and triethyl orthoformate or dimethylformamide diethyl acetal, as previously reported).[10] No C-2 proton exchange was observed in D_2O solutions of **6a**, whereas treatment with *n*-BuLi (THF, −78 °C) afforded an orange-red solution that was quenched with D_2O to show, in the ^1H NMR spectrum of the products taken before further work-up, the disappearance of the signal at δ 6.95 (1H, s) assigned to C-2(H) and no change in intensity of other signals, confirming exclusive deprotonation at C-2. Encouraged by this observation, we prepared the 1-(2-phenoxyethyl)- and 1-(2-methoxyethyl)-4,5-dihydroimidazoles **6b** (76%) and **6c** (50%), respectively, from the corresponding diamines and triethyl orthoformate. We anticipated that these oxygen-containing N-1 substituents might assist lithiation by coordination.[11] Deprotonation at C-2 was observed as for the 1-benzyl compound **6a**, however these systems offered no advantage over **6a** so studies were continued largely using this 1-benzyl-4,5-dihydroimidazole.



Initial attempts at direct alkylation of the presumed lithio-dihydroimidazoles **7** with simple haloalkane alkyl electrophiles offered mixed success. Deprotonation of **6a** as described above with *n*-BuLi, followed by reaction with iodomethane led to the corresponding 2-methyl derivative **8a** (50%). Similar treatment of the 1-(2-methoxyethyl) heterocycle **6c** afforded the 2-methyl compound **8b** (34%); in addition a low yield of the 2-ethyl material **8c** (7%) was also recovered indicating a lateral α-deprotonation, presumably by proton-exchange of the 2-methyl group of the first-formed **8b** with the corresponding 2-lithio derivative **7**, followed by an α-methylation before the desired C-2 alkylation was complete.[11] The use of haloalkanes other than the reactive iodomethane was unsuccessful, and there was no improvement by addition of dipolar aprotic solvent (HMPA), or by changing to toluene-4-sulfonate or trifluoro methanesulfonate electrophiles. Alkylation of **6a** was successful with dimethyl sulfate to produce **8a** (60%) but this did not translate to other dialkyl sulfates. Transmetallation from lithium with pentynylcopper or chlorotitanium triisopropoxide did not improve the alkylation, and 2-triakylsilyl or 2-trialkylstannyl derivatives (potential masked carbanions) were not recovered from reaction of **7** (R^1=CH_2Ph) with chlorosilanes or -stannanes.

With the unreliability of alkylation with electrophiles, we modified our strategy to utilise the nucleophilic lithio-dihydroimidazole **7** in conjunction with nucleophilic organometallic alkylating agents, so a double umpolung of the inherent electrophilic reactivity of C-2 of dihydroimidazoles. We thus planned to use the nucleophilic C-2 species to provide an activated electrophilic C-2 for substitution. This required a C-2 substituent available both as an electrophile and as a nucleofugal leaving group. To meet these demands we selected the phenylthio group, available as an electrophile in disulfides or sulfenyl chlorides, and with leaving group potential as the phenylthiolate anion. We were pleased to find that the 2-lithio dihydroimidazole **7** (R^1=CH_2Ph) formed from 1-benzyl compound **6a** reacted efficiently with diphenyl disulfide to yield the 2-phenylthio compound **9a** (Scheme 1). When isolation of **9a** was continued via aqueous workup, the yield was moderate (56%) but also isolated was 1-benzyltetrahydroimidazole-2-one **10** (25%), presumably derived by adventitious hydrolysis during isolation. This process must involve substitution of 2-phenylthio group by an oxygen nucleophile, so supporting our choice of sulfenylation. Although tetrahydroimidazole **9a** was unreactive towards Grignard nucleophiles, it did react with *n*-BuLi (THF, −78 °C) to displace the phenylthio group and afford 1-benzyl-2-butyl-4,5-dihydroimidazole **11a** in good yield (70%) (Scheme 1).[12] The distinctive value of arylthio as leaving group in this sequence was apparent when di-*n*-butyl disulfide was used as electrophile with **7** (R^1=CH_2Ph) to prepare 2-butylthio compound **9b** (63%) with no observed hydrolysis to the imidazolone **10**, but then **9b** proved inert towards *n*-butyl-lithium. There was no reaction of **7** (R^1=CH_2Ph) with di-*tert*-butyl disulfide as electrophile.



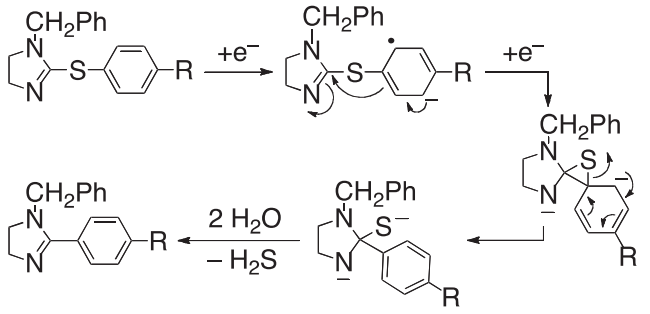
Scheme 1. Reagents: i, *n*-BuLi, −78 °C, THF; R^1SSR^1; ii, R^2Li, −78 °C, THF; iii, 2 *sec*-BuLi, −78 °C, THF.

We have reported elsewhere on an alternative approach to 1-benzyl-2-methylthio-4,5-dihydroimidazoles by reacting *N*-benzyl-1,2-diaminoethane with 1,1′-thiocarbonyldiimidazole to give 1-benzyl-2,3,4,5-tetrahydroimidazol-2-thione, followed by S-alkylation with iodomethane,[13] but this is clearly not applicable to 2-phenylthio compound **9a**.

In order to avoid the losses of 2-phenylthiodihydroimidazole **9a** due to hydrolysis during isolation and to generate a direct C-2 alkylation protocol, the sulfenylation and substitution were telescoped and performed in a one-pot protocol. Thus 1-benzyl-4,5-dihydroimidazole **6a** was treated in succession with *n*-BuLi and diphenyl disulfide (THF, −78 °C), the solution warmed to 20 °C to complete sulfenylation and then recooled to −78 °C before addition of an alkyl-lithium. The sequence was completed by conventional work-up and chromatography, and used to prepare the 2-butyl-, 2-octyl- and 2-phenyl-4,5-dihydroimidazoles **11a**–**c** (72, 76 and 52%, respectively, based on **6a**). 2-Furyl compound **11d** was also prepared in a low, unoptimised yield.

An unexpected result was observed when we attempted to extend this protocol to a secondary alkyl-lithium. Treatment of the 2-phenylthio compound **6a** with *sec*-BuLi (2 mol equiv, THF, −78 °C) did not give a substitution product but afforded 1-benzyl-2-phenyl-4,5-dihydroimidazole **11c** (69%) (Scheme 1). This suggested that the phenylthio compound had undergone a sulfur extrusion. We next prepared the 2-(4-methylphenyl)thio-4,5-dihydroimidazole **9c** (55%) from the 2-H compound **6a** by lithiation and sulfenylation (*n*-BuLi, THF, −78 °C; bis(4-methylphenyl) disulfide); some urea **10** was again also isolated (21%). Sulfide contraction of **9c** using *sec*-BuLi as above gave 1-benzyl-2-(4-methylphenyl)-4,5-dihydroimidazole **12** (46%). The position of the methyl substitution could be easily determined by from the diagnostic doublet signals (J=7) for a 1,4-disubstituted benzene in the ^{1}H NMR spectrum at δ 7.3 and 7.5, each 2H.

The regiospecific nature of this sulfide contraction leads us to suggest the mechanism outlined in Scheme 2. We propose a single electron transfer from the secondary alkyl-lithium to the C-2 substituent aryl ring to afford a radical anion in a process analogous to the Birch reduction.[14] In the absence of a proton source, the radical anion can rearrange to an episulfide, thus transferring the negative charge to an electronegative nitrogen atom. A further one-electron reduction and aromatisation by expulsion of the sulfur atom leads to an *N*,*S*-dianion that on aqueous work-up we propose will undergo protonation and elimination of H_2S to regenerate the dihydroimidazole ring.



Scheme 2. Proposed mechanism for sulfide contraction of 2-arylthio-4,5-dihydroimidazoles using *sec*-BuLi.

3. Conclusions

We have therefore discovered a route to the alkylation of 4,5-dihydroimidazoles at C-2 (unreliable using direct methods) using a double umpolung of the inherent reactivity of that position, via sulfenylation of a nucleophilic C-2 lithio-species and substitution using an alkyl nucleophile. Arylation via an unexpected sulfide contraction from the arylsulfenylation products has also been demonstrated. When these 2-(aryl/alkyl)-4,5-dihydroimidazoles are cleaved as we have reported, to carboxylic acids or ketones, this completes a single-carbon transfer that mimics the tetrahydrofolate coenzyme family. Our studies using higher oxidation level electrophiles, that mimic the actions of thiamine, will be reported separately.

4. Experimental section

4.1. General

Melting points were obtained on a Gallenkamp capillary or a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded using Pye Unicam SP1000 or SP3-100 spectrometers. Mass spectra were recorded using AEI MS902 or VG 7070E spectrometers. ^{1}H NMR spectra were obtained using the following spectrometers as indicated: Perkin–Elmer R32 or Joel FX90Q spectrometers at 90 MHz. ^{13}C NMR spectra were recorded using a Jeol FX90Q spectrometer at 22.7 MHz. ^{1}H NMR spectra were determined in $CDCl_3$ solution and chemical shifts δ_C quoted in parts per million (ppm) from TMS as internal standard. Coupling constants J are quoted in hertz with multiplicities: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet and br-broad. ^{13}C NMR spectra were determined in $CDCl_3$ solution and chemical shifts δ_C quoted in ppm from TMS as internal standard or from TMS using $CDCl_3$ as internal standard. Column chromatography was carried out at medium pressure using Merck Kieselgel 60 (Art. 9385); TLC was carried out on silica plates (Kieselgel 60, F_{254}, Merck Art. 5554). Solvent extractions were dried over anhydrous $MgSO_4$ or Na_2SO_4 for at least 10 min. Ether refers to diethyl ether and light petroleum to the fraction of bp 60–80 °C. THF and ether were distilled from $LiAlH_4$ or potassium immediately prior to use. Other dry solvents were prepared as described in Perrin et al.[15] Alkyl-lithiums were standardised by the diphenylacetic acid method.[16]

4.2. Preparation of dihydroimidazoles (6)

*4.2.1. 1-Benzyl-4,5-dihydroimidazole (**6a**).* *N*-Benzyl-1,2-diaminoe thane (42.9 g, 0.290 mol), triethyl orthoformate (169 g, 1.14 mol) and toluene-4-sulfonic acid (1.00 g, 5.75 mmol) were heated together under reflux for 20 h. The cooled solution was basified with aqueous NaOH solution (5% w/v, 50 mL) and extracted with $CHCl_3$ (2×250 mL). The organic extracts were dried and concentrated under reduced pressure and the residue was distilled to afford to afford the title compound **6a** (34.3 g, 75%) as a colourless oil that solidified on standing, mp 45–46 °C having data as reported.[10]

*4.2.2. 1-(2-Phenoxyethyl)-4,5-dihydroimidazole (**6b**).* 2-Bromoethyl phenyl ether (21.1 g, 0.105 mol) was added dropwise to 1,2-diaminoethane (32.0 g, 0.520 mol) and the mixture heated under reflux for 8 h. The cooled mixture was extracted with ether (2×200 mL) and the organic extracts were dried, concentrated under reduced pressure and the residue was distilled to afford *N*-(2-phenoxyethyl)-1,2-diaminoethane (13.7 g, 72%) as a colourless oil, bp 126 °C at 1.5 mmHg; ν_{max} (film)/cm^{-1} 3300, 3020, 2930, 1600, 1490, 1460, 1250, 1050, 750; δ_C 7.30–7.34 (2H, m, Ar–H), 6.94–6.96 (3H, m, Ar–H), 4.02 (2H, t, J=5.5, OCH_2), 2.95 (2H, t, J=5.5, NCH_2), 2.70–2.73 (4H, m, NCH_2CH_2N), 1.31 (3H, s, NH, NH_2); m/z (M^+ not present) 150 (100%), 121 (14), 94 (10), 66 (36), 77 (24), 56 (76), 44 (73). *N*-(2-Phenoxyethyl)-1,2-diaminoethane (13.0 g, 72.5 mmol) was treated with triethyl orthoformate and toluene-4-sulfonic acid according to the method described above for the preparation of **6a** to afford the title compound **6b** (10.5 g, 76%) as a colourless oil after distillation, bp 160 °C at 2.5 mmHg; ν_{max} (CCl_4)/cm^{-1} 3040, 2970, 2930, 1600, 1220, 1050; δ_C 7.33–7.36 (2H, m, Ar–H), 6.90–6.94 (4H, m, Ar–H, 2-CH), 4.11 (2H, t, J=5.3, OCH_2), 3.78 (2H, t, J=9.2, NCH_2CH_2N), 3.52 (2H, t, J=5.3, OCH_2CH_2), 3.30 (2H, t, J=9.2, NCH_2CH_2N); δ_C 158.4, 157.6 (Ar–C), 129.5, 121.2, 114.6 (Ar–CH), 66.1 (OCH_2), 55.2, 47.0, 46.7 (CH_2); m/z 190 (M^+, 49%), 63 (100), 77 (12), 56 (69). HRMS: M^+ 190.1112; $C_{11}H_{14}N_2O$ requires M^+ 190.1106.

*4.2.3. 1-(2-Methoxyethyl)-4,5-dihydroimidazole (**6c**).* The method described above for preparation of *N*-(2-phenoxyethyl)-1,2-diaminoethane was followed, but using 2-chloroethyl methyl ether (14.0 g, 0.150 mol) and 1,2-diaminoethane (30.0 g, 0.60 mol) to afford *N*-(2-methoxyethyl)-1,2-diaminoethane (14.6 g, 83%) as a colourless oil after distillation, bp 66 °C at 2 mmHg; ν_{max} (film)/cm^{-1} 3300, 2880, 1460, 1115; δ_C 3.55 (2H, t, J=5.3, OCH_2), 3.42 (3H, s, CH_3), 3.28–3.35 (6H, m, $CH_2NCH_2CH_2N$), 1.35 (3H, s, NH, NH_2); m/z (M^+ not present) 88 (100%), 73 (17), 59 (26), 44 (51). *N*-(2-Methoxyethyl)-1,2-diaminoethane (11.8 g, 0.100 mol) was treated

with triethyl orthoformate (59.2 g, 0.400 mol) and toluene-4-sulfonic acid (0.350 g, 2.00 mmol) according to the method described above for the preparation of **6a** to afford the title compound **6c** (6.89 g, 50%) as a colourless oil after distillation, bp 84 °C at 0.5 mmHg; ν_{max} (film)/cm^{-1} 2920, 2860, 1600, 1200, 1120; δ_C 6.95 (1H, s, 2-CH), 3.91 (2H, t, J=9.0, NCH_2CH$_2$N), 3.35–3.43 (9H, m, CH$_3$OCH$_2$CH$_2$N, NCH$_2$CH_2N); δ_C 157.8 (C-2), 70.75 (OCH$_3$), 58.8, 55.0, 49.0, 47.3 (CH$_2$); m/z 128 (M$^+$, 28%), 101 (13), 88 (25), 83 (100), 56 (55). HRMS: M$^+$ 128.0947; $C_6H_{12}N_2O$ requires M$^+$ 128.0950.

4.3. C-2 Alkylation products (8)

*4.3.1. 1-Benzyl-2-methyl-4,5-dihydroimidazole (**8a**)*

4.3.1.1. Method A. *n*-Butyl-lithium (1.42 M solution in hexanes; 7.00 mL, 10.0 mmol) was added dropwise to a solution of 1-benzyl-4,5-dihydroimidazole **6a** (1.60 g, 10.0 mmol) in dry THF (50 mL), precooled to −78 °C under an atmosphere of nitrogen. After 20 min at this temperature, iodomethane (1.42 g, 10.0 mmol) was added dropwise and the mixture was allowed to warm to 20 °C and stirred for a further 4 h. The mixture was concentrated under reduced pressure, the residue was partitioned between CHCl$_3$ (50 mL) and water (50 mL) and the organic layer was dried and concentrated under reduced pressure to afford, after Kugelrohr distillation, the title compound **8a** (0.87 g, 50%) as a pale yellow oil, bp 120 °C (oven temperature) at 2 mmHg (lit.,[17] bp 102–106 °C at 1 mmHg); ν_{max} (film)/cm^{-1} 2920, 2850, 1600, 1430, 1270, 940, 740, 710; δ_C 7.2.9–7.31 (5H, m, Ar–H), 4.30 (2H, s, CH_2Ph), 3.75, 3.25 (each 2H, t, J=8.9, NCH$_2$CH$_2$N), 2.01 (3H, s, CH$_3$). HRMS: M$^+$ 174.1151; $C_{11}H_{14}N_2$ requires M$^+$ 174.1157.

4.3.1.2. Method B. Performed according to method A described above but using 1-benzyl-4,5-dihydroimidazole **6a** (0.62 g, 3.88 mmol) in dry THF (30 mL), *n*-butyl-lithium (1.50 M solution in hexanes; 2.78 mL, 4.16 mmol) and dimethyl sulfate (0.525 g, 4.16 mmol), purification by column chromatography eluting with CHCl$_3$/2-aminopropane (99.5:0.5 v/v) afforded the title compound **8a** (0.41 g, 60%) as a colourless oil identical to a sample prepared by method A.

*4.3.2. 1-(2-Methoxyethyl)-2-methyl-4,5-dihydroimidazole (**8b**).* Compound (**8b**) was prepared by method A described above for the preparation of **8a** but using 1-(2-methoxyethyl)-4,5-dihydroimidazole **6c** (2.61 g, 20.0 mmol), *n*-butyl-lithium (1.40 M solution in hexanes; 16.5 mL, 23.0 mmol) and iodomethane (3.20 g, 22.0 mmol). Column chromatography eluting with CHCl$_3$/2-aminopropane (99.5:0.5 v/v) afforded the title compound **8b** (1.01 g, 34%) as a colourless oil that was not further purified; ν_{max} (film)/cm^{-1} 2940, 2860, 1650, 1600, 1400, 1200, 1120; δ_C 3.36–3.42 (11H, m, CH$_3$OCH$_2$CH$_2$N, NCH$_2$CH$_2$N), 2.00 (3H, s, CH$_3$). Also isolated was 1-(2-methoxyethyl)-2-ethyl-4,5-dihydroimidazole **8c** (0.20 g, 7%) that was not further purified; δ_C 3.37–3.43 (11H, m, CH$_3$OCH$_2$CH$_2$N, NCH$_2$CH$_2$N), 2.24 (2H, q, J=7.5, CH_2CH$_3$), 1.20 (3H, t, J=7.5, CH$_2$CH_3).

4.4. 2-Aryl- and 2-alkylthiodihydroimidazoles (9)

*4.4.1. 1-Benzyl-2-phenylthio-4,5-dihydroimidazole (**9a**).* To 1-benzyl-4,5-dihydroimidazole **6a** (2.18 g, 13.6 mmol) in dry THF (30 mL) stirred at −78 °C under an atmosphere of nitrogen was added *n*-butyl-lithium (1.5 M solution in hexanes; 9.75 mL, 14.6 mmol). After 20 min diphenyl disulfide (3.20 g, 14.6 mmol) in dry THF (5 mL) was added dropwise and the mixture was maintained at −78 °C for 2 h, then allowed to warm to 20 °C, stirred for a further 30 min and the reaction was quenched by the addition of water (2 mL). The mixture was concentrated under reduced pressure and partitioned between CHCl$_3$ (2×50 mL) and water (50 mL). The combined organic extracts were dried, concentrated under reduced pressure and the residue was purified by column chromatography eluting with CHCl$_3$/2-aminopropane (99.5:0.5 v/v) to afford the title compound **9a** (2.05 g, 56%) as a colourless oil; ν_{max} (film)/cm^{-1} 3060, 2950, 2860, 1560, 1160, 1030, 750, 705; δ_C 7.58–7.62 (2H, m, Ar–H), 7.25–7.35 (8H, m, Ar–H), 4.35 (2H, s, CH_2Ph), 3.69–3.71, 3.24–3.26 (each 2H, m, NCH$_2$CH$_2$N); δ_C 162.7 (C-2), 136.5, 133.4 (Ar–C), 128.4, 128.2, 128.0, 127.2, 127.1, 126.9 (Ar–CH), 52.9, 51.0, 50.0 (CH$_2$); m/z 268 (M$^+$, 36%), 267 (92), 207 (15), 121 (23), 91 (100), 65 (21), 51 (82). HRMS: M$^+$ 268.1027; $C_{16}H_{16}N_2S$ requires M$^+$ 268.1034. Also isolated was 1-benzyl-2,3,4,5-tetrahydroimidazol-2-one **10** (0.60 g, 25%) as a colourless needles, mp 129–130 °C (lit.[12] mp 124–127 °C); ν_{max} (KBr)/cm^{-1} 3350, 2980, 1720, 1520, 1220, 1040, 710; δ_C 7.37–7.43 (5H, m, Ar–H), 6.10 (1H, br s, NH), 4.45 (2H, s, CH_2Ph), 3.38–3.43 (4H, m, NCH$_2$CH$_2$N); δ_C 162.9 (CO), 136.9 (Ar–C), 128.2, 127.6, 127.0 (Ar–CH), 47.3, 44.2, 37.7 (CH$_2$); m/z 176 (M$^+$, 87%), 175 (23), 147 (25), 105 (14), 104 (34), 99 (24), 91 (100), 85 (26), 65 (26), 51 (10). HRMS: M$^+$ 176.0946; $C_{10}H_{12}N_2O$ requires M$^+$ 176.0950.

*4.4.2. 1-Benzyl-2-butylthio-4,5-dihydroimidazole (**9b**).* Compound (**9b**) was prepared by the method described above for the preparation of **9a** but using 1-benzyl-4,5-dihydroimidazole **6a** (1.00 g, 6.25 mmol) and di-*n*-butyl disulfide (1.23 g, 6.87 mmol) to afford the title compound **9b** (0.98 g, 63%) as a pale yellow oil; ν_{max} (film)/cm^{-1} 3030, 2960, 2930, 2860, 1565, 1460, 1300, 1190, 710; δ_C 7.22–7.28 (5H, m, Ar–H), 4.25 (2H, s, CH_2Ph), 3.75 (2H, t, J=9.0, NCH_2CH$_2$N), 3.16–3.24 (4H, m, NCH$_2$CH_2N, SCH_2), 1.52–1.58 (4H, m, CH_2CH$_2$CH$_3$), 0.90 (3H, t, J=7.1, CH$_3$); δ_C 164.6 (C-2), 137.2 (Ar–C), 128.4, 127.6, 127.2 (Ar–CH), 53.2, 51.2, 50.7, 31.3, 31.2, 21.8 (CH$_2$), 13.5 (CH$_3$); m/z 248 (M$^+$, 6%), 192 (100), 191 (53), 159 (15), 91 (47), 44 (11). HRMS: M$^+$ 248.1343; $C_{14}H_{20}N_2S$ requires M$^+$ 248.1347.

*4.4.3. 1-Benzyl-2-(4-methylphenyl)-4,5-dihydroimidazole (**9c**).* Compound (**9c**) was prepared by the method described above for the preparation of **9a** but using 1-benzyl-4,5-dihydroimidazole **6a** (0.770 g, 4.81 mmol) and di-(4-methylphenyl) disulfide (1.30 g, 5.30 mmol) to afford the title compound **9c** (0.74 g, 55%) as a pale yellow oil; δ_C 7.45 (2H, d, J=7, Ar–H), 7.23–7.27 (5H, m, Ar–H), 7.10 (2H, J=7, Ar–H), 4.30 (2H, s, CH_2Ph), 3.65, 3.15 (each 2H, t, J=9.2, NCH$_2$CH$_2$N), 2.3 (3H, s, CH$_3$); δ_C 153.3 (C-2), 133.8, 137.0, 125.0 (Ar–C), 134.3, 129.7, 128.3, 127.5, 127.2 (Ar–CH), 53.3, 51.4, 50.6 (CH$_2$), 20.9 (CH$_3$); m/z 282 (M$^+$, 22%), 281 (31), 246 (100), 161 (18), 123 (98), 91 (99), 83 (19), 77 (20), 65 (16). HRMS: M$^+$ 282.1180; $C_{17}H_{18}N_2S$ requires M$^+$ 282.1191. Also isolated was 1-benzyl-2,3,4,5-tetrahydroimidazol-2-one **10** (0.18 g, 21%) identical to the sample described above.

4.5. 1-Benzyl-2-butyl-4,5-dihydroimidazole (11a)

To a solution of 1-benzyl-2-phenylthio-4,5-dihydroimidazole **9a** (0.710 g, 2.65 mmol) in dry THF (15 mL) cooled to −78 °C under an atmosphere of nitrogen, was added *n*-butyl-lithium (1.47 M solution in hexanes; 2.00 mL, 2.92 mmol). The mixture was stirred at this temperature for 2 h, the reaction was quenched by the addition of water (0.5 mL) and allowed to warm to 20 °C. The mixture was partitioned between CHCl$_3$ (2×30 mL) and water (30 mL), the combined organic extracts were dried and concentrated under reduced pressure and the residue was purified by column chromatography eluting with CHCl$_3$/2-aminopropane (99.5:0.5 v/v) to afford the title compound **11a** (0.40 g, 70%) as a colourless oil; ν_{max} (film)/cm^{-1} 3040, 2950, 1610, 1450, 1420, 1250, 750; δ_C 7.23–7.27 (5H, m, Ar–H), 4.25 (2H, s, CH_2Ph), 3.70, 3.15 (each 2H, t, J=9.1, NCH$_2$CH$_2$N), 2.30 (2H, t, J=7.0, CH$_2$), 1.46–1.52 (4H, m, CH_2CH$_2$CH$_3$), 0.90 (3H, t, J=7.1, CH$_3$); δ_C 167.1 (C-2), 137.9 (Ar–C), 128.7, 127.3,

127.2 (Ar–CH), 52.2, 50.8, 50.3 (CH_2N), 28.7, 27.6, 22.6 (CH_2), 13.8 (CH_3); *m*/*z* (M^+, 19%), 187 (18), 175 (10), 174 (80), 173 (100), 91 (98), 65 (15), 56 (11), 42 (11). HRMS: M^+ 216.1627; $C_{14}H_{20}N_2$ requires M^+ 216.1626.

4.6. One-pot C-2 alkylation of 1-benzyl-4,5-dihydroimidazole (6a)

*4.6.1. 1-Benzyl-2-butyl-4,5-dihydroimidazole (**11a**).* To 1-benzyl-4,5-dihydroimidazole **6a** (0.750 g, 4.68 mmol) in dry THF (30 mL) stirred at −78 °C under an atmosphere of nitrogen was added *n*-butyl-lithium (1.47 M solution in hexanes; 3.20 mL, 4.68 mmol). After 20 min diphenyl disulfide (1.02 g, 4.68 mmol) in dry THF (5 cm^3) was added dropwise and the solution was maintained at −78 °C for 1 h then allowed to warm to 20 °C, stirred for a further 10 min and cooled to −78 °C before *n*-butyl-lithium (1.47 M solution in hexanes; 3.50 mL, 5.16 mmol) was added dropwise and the mixture stirred for a further 1.5 h at −78 °C. The mixture was allowed to warm to 20 °C, the reaction was quenched by the addition of water (2.0 mL) and concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ (2×75 mL) and water (75 mL) and the combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with $CHCl_3$/2-aminopropane (99.25:0.75 v/v) to afford the title compound **11a** (0.73 g, 72%) as pale yellow oil, identical to the sample described above.

*4.6.2. 1-Benzyl-2-octyl-4,5-dihydroimidazole (**11b**).* Compound (**11b**) was prepared using the method described above for the 'one-pot' preparation of **11a** but using 1-benzyl-4,5-dihydroimidazole **6a** (0.750 g, 4.68 mmol) and *n*-octyl-lithium (0.41 M solution in pentane; 16.0 mL, 6.55 mmol) to afford after column chromatography eluting with $CHCl_3$/2-aminopropane (99.5:0.5 v/v), the title compound **11b** (0.97 g, 76%) as a colourless oil; ν_{max} (film)/cm^{-1} 3040, 2940, 2860, 1670, 1610, 1460, 1420, 1250, 740; δ_C 7.27–7.32 (5H, m, Ar–H), 4.30 (2H, s, CH_2Ph), 3.70, 3.20 (each 2H, t, *J*=8.9, NCH_2CH_2N), 2.30 (2H, t, *J*=7.0, CH_2), 1.26–1.34 (12H, m, 6× CH_2), 0.90 (3H, t, *J*=7.1, CH_3); δ_C 166.4 (C-2), 137.3 (Ar–C), 128.0, 126.8, 126.6 (Ar–CH), 51.6, 50.2, 49.7, 31.2, 28.9, 28.7, 28.6, 27.3, 26.0, 22.0 (CH_2), 13.5 (CH_3); *m*/*z* 272 (M^+, 19%), 229 (23), 188 (17), 187 (17), 174 (96), 173 (89), 120 (10), 91 (100), 83 (10), 51 (10). HRMS: M^+ 272.2254; $C_{18}H_{28}N_2$ requires M^+ 272.2252.

*4.6.3. 1-Benzyl-2-phenyl-4,5-dihydroimidazole (**11c**).* Compound (**11c**) was prepared using the method described above for the 'one-pot' preparation of **11a** but using 1-benzyl-4,5-dihydroimidazole **6a** (0.750 g, 4.68 mmol) and phenyl-lithium (1.70 M solution in cyclohexane/ether; 8.80 mL, 15.0 mmol) to afford after column chromatography eluting with $CHCl_3$/2-aminopropane (99.25:0.75 v/v), the title compound **11c** (1.52 g, 52%) as a colourless solid, mp 64–65 °C; δ_C 7.70–7.72 (2H, m, Ar–H), 7.38–7.42 (8H, m, Ar–H), 4.30 (2H, s, CH_2Ph), 3.95, 3.40 (each 2H, t, *J*=9.0, NCH_2CH_2N); δ_C 166.7 (C-2), 137.6, 131.0 (Ar–C), 129.3, 128.1, 127.9, 127.6, 126.8, 126.6 (Ar–CH), 53.0, 52.6, 50.6 (CH_2); *m*/*z* 236 (M^+, 53%), 235 (12), 117 (100), 91 (50), 77 (16). HRMS: M^+ 236.1319; $C_{16}H_{16}N_2$ requires M^+ 236.1313.

*4.6.4. 1-Benzyl-2-(2-furyl)-4,5-dihydroimidazole (**11d**).* Compound (**11d**) was prepared using the method described above for the 'one-pot' preparation of **11a** but using 1-benzyl-4,5-dihydroimidazole **6a** (1.00 g, 6.25 mmol) and 2-furyl-lithium prepared from furan (0.638 g, 9.38 mmol) and *n*-butyl-lithium (1.40 M solution in hexanes; 6.70 mL, 9.38 mmol) in dry THF (25 mL) to afford after column chromatography eluting with $CHCl_3$/2-aminopropane (99.5:0.5 v/v), the title compound **11d** (0.15 g, 11%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2920, 1580, 1410, 1200, 1030; δ_C 7.48 (1H, d, *J*=1.1, Fur–H), 7.28–7.32 (5H, m, Ar–H), 6.90 (1H, d, *J*=3.3, Fur–H), 6.45 (1H, dd, *J*=3.3. 1.1, Fur–H), 4.60 (2H, s, CH_2Ph), 3.90, 3.40 (each 2H, t, *J*=8.8, NCH_2CH_2N); δ_C 157.2 (C-2), 145.7 (Fur–C), 143.6 (Fur–CH), 138.1 (Ar–C), 128.7, 127.4, 127.2 (Ar–CH), 113.0, 111.3 (Fur–CH), 53.4, 52.3, 51.3 (CH_2); *m*/*z* 226 (M^+, 50%), 225 (11), 135 (15), 108 (26), 107 (36), 91 (100), 65 (14). HRMS: M^+ 226.1102; $C_{14}H_{14}N_2O$ requires M^+ 226.1106.

4.7. Sulfur extrusion reactions using *sec*-butyl-lithium

*4.7.1. 1-Benzyl-2-phenyl-4,5-dihydroimidazole (**11c**).* To 1-benzyl-2-phenylthio-4,5-dihydroimidazole **9a** (450 mg, 1.68 mmol) in dry THF (10 mL) stirred at −78 °C under an atmosphere of nitrogen was added *sec*-butyl-lithium (1.40 M solution in cyclohexane; 2.60 mL, 3.67 mmol). The mixture was maintained at −78 °C for 1.5 h, allowed to warm to 20 °C and stirred for a further 5 min when the reaction was quenched by the addition of water (2.0 mL) and the mixture was partitioned between $CHCl_3$ (2×50 mL) and water (50 mL). The combined organic extracts were dried, concentrated under reduced pressure and the residue was purified by column chromatography eluting with $CHCl_3$/2-aminopropane (99.5:0.5 v/v) to afford the title compound **11c** (274 mg, 69%) as a colourless solid identical to the sample described above.

*4.7.2. 1-Benzyl-2-(4-methylphenyl)-4,5-dihydroimidazole (**12**).* Compound (**12**) was prepared using the method described above for the preparation of **11c** but using 1-benzyl-2-(4-methylphenylthio)-4,5-dihydroimidazole (492 mg, 1.74 mmol) and *sec*-butyl-lithium (1.40 M solution in cyclohexane; 2.75 mL, 3.88 mmol) to afford the title compound **12** (198 mg, 46%) as a pale yellow waxy solid; ν_{max} (film)/cm^{-1} 3040, 290, 2880, 1605, 1410, 1285, 1260, 1020, 845, 760; δ_C 7.50 (2H, d, *J*=7.0, Ar–H), 7.28–7.32 (2H, d, *J*=7.0, & 5H, m, Ar–H), 4.25 (2H, s, CH_2Ph), 3.90, 3.30 (each 2H, t, *J*=9.0, NCH_2CH_2N), 2.35 (3H, s, CH_3); δ_C 167.3 (C-2), 139.7, 138.1, 128.3 (Ar–C), 129.0, 123.5, 128.0, 127.1, 126.0 (Ar–CH), 53.2, 53.1, 50.9 (CH_2), 21.2 (CH_3); *m*/*z* 250 (M^+, 72%), 249 (22), 131 (100), 91 (93), 65 (12). HRMS: M^+ 250.1461; $C_{17}H_{18}N_2$ requires M, 250.1470.

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