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TETRAHYDROFOLATE COENZYME MODELS: IMIDAZOLINES AS NUCLEOPHILIC C_1-TRANSFER REAGENTS

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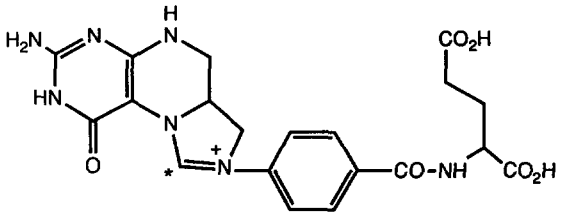
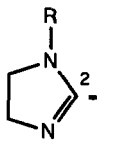
Summary: 1-Benzyl-2-imidazoline is deprotonated at C-2 and alkylated by a sulphenylation-substitution sequence (to complete a formal C_1-transfer), whereas arylation occurs by an unusual sulphenylation-sulphide contraction pathway

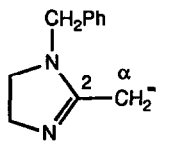
The 2-imidazoline (4,5-dihydroimidazole) ring of the coenzyme N^5,N^{10}-methenyltetrahydrofolate (1) is involved in Nature in the transfer of a single carbon unit at the *carboxylate* (and other) oxidation levels.[1] We have been developing methods to mimic such processes.[2] In these and in the biological situation the transferred carbon **C*** (C-2 of the imidazoline sub-unit) acts as an electrophile, and this polarity is also used in the methods for transfer at the *carbonyl* oxidation level reported by ourselves and others.[3,4] We wished instead to employ C-2 of an imidazoline initially as a nucleophile (2) in an extension to **C_1-transfer** of our C_2-transfer process based on α-deprotonation (3).[2c] We report herein the implementation of this strategy for C-2 alkylation of an imidazoline *via* a one-pot sulphenylation-alkylation sequence; we also report C-2 arylation via an unexpected sulphide contraction.[5] Combined with cleavage of the ring by hydrolysis,[2c] this completes a C_1-transfer at the carboxylate oxidation level; our alternative cleavage sequence[3b] would lead to ketones.



(1)

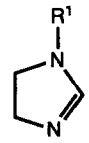


(2)

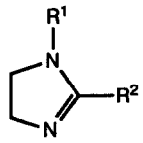


(3)

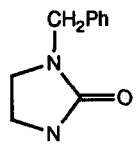
As substrate we prepared 1-benzyl-2-imidazoline (4a)[6] from N-benzyl-1,2-diaminoethane[7] and triethyl orthoformate (4 mol. equiv.; p-TsOH, 0.05 mol. equiv.; 72%). No exchange was observed at C-2 when (4a) was dissolved in D_2O. On the other hand treatment with n-BuLi (THF, -78°C, 20 min) led to an orange-red solution; exclusive deprotonation at C-2 was confirmed by quenching with D_2O, when examination of the products before further work-up showed complete disappearance of the C-2 signal at δ 6.95 (1H, s) in the ^1H n.m.r. spectrum and no change in intensity of other signals.[8] We also prepared the 1-(2-phenoxyethyl)- and 1-(2-methoxyethyl)-imidazolines, (4b) (76%) and (4c) (50%) respectively,[6] from the corresponding diamines[9] and triethyl orthoformate. These were designed so that the oxygen atom could assist lithiation by coordination, and indeed C-2 deprotonation occurred as for (4a), but these new systems offered no advantage over the 1-benzyl compound (4a).[10]



(4) a; R^1= CH_2Ph
b; R^1= CH_2CH_2OPh
c; R^1= CH_2CH_2OMe



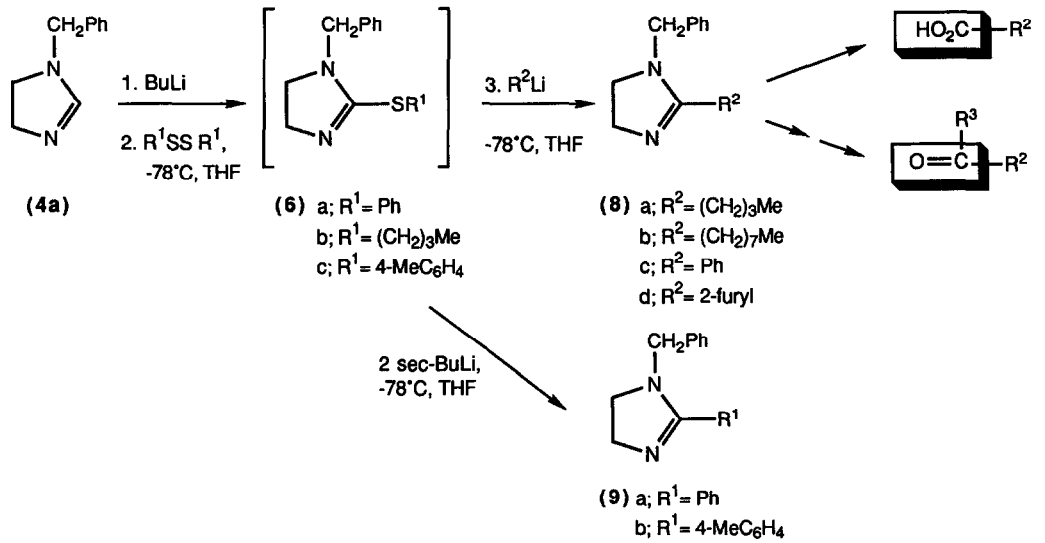
(5) a; R^1= CH_2Ph, R^2= Me
b; R^1= CH_2CH_2OMe, R^2= Me
c; R^1= CH_2CH_2OMe, R^2= Et



(7)

Alkylation experiments with the 2-lithio-imidazolines met with mixed success. Treatment of (4a) with n-BuLi as above, followed by iodomethane led to the 2-methyl derivative (5a)[11] in moderate yield (50%); similar treatment of (4c) led to the 2-methyl compound (5b) (34%).[6] A low yield (7%) of the 2-ethyl compound (5c)[6] was also observed, indicating that the basic 2-lithio-imidazoline (2) could α-deprotonate initially formed (5b), which undergoes a second methylation before completion of the desired alkylation.[12]

Lithiation-alkylation of (4a) with other alkyl halides was unsuccessful. Addition of dipolar aprotic solvents such as HMPA afforded no improvement; neither did the use of alkyl tosylates or triflates as electrophile.[13] Methylation was achieved with dimethyl sulphate (60%) but other dialkyl sulphates failed to react. Trans-metallation of the 2-lithio-derivative from (4a) using pentynyl copper[14] or chlorotitanium triisopropoxide had no effect on the alkylation and 2-trialkylsilyl or 2-trialkylstannyl derivatives (potential masked carbanions) were not observed from reaction of the 2-lithio-imidazoline with the corresponding chloro-silanes or -stannanes.[15]



(4a)

(6) a; R^1= Ph
b; R^1= $(CH_2)_3Me$
c; R^1= 4-MeC_6H_4

(8) a; R^2= $(CH_2)_3Me$
b; R^2= $(CH_2)_7Me$
c; R^2= Ph
d; R^2= 2-furyl

(9) a; R^1= Ph
b; R^1= 4-MeC_6H_4

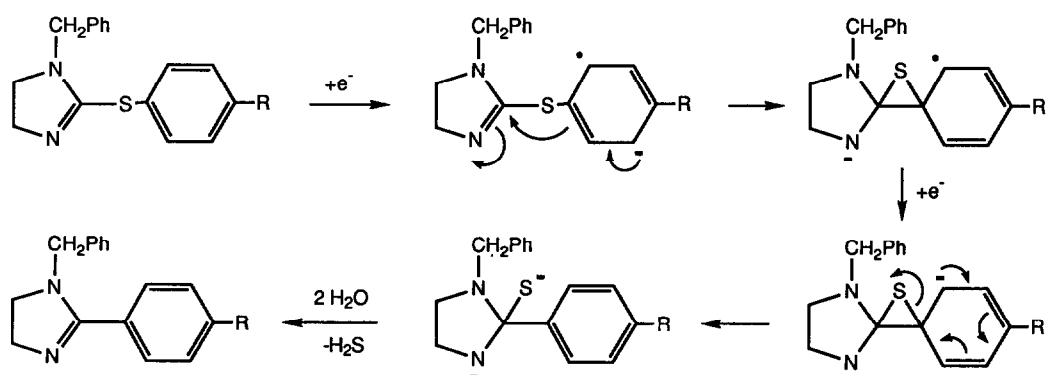
Scheme 1

We determined therefore to use our nucleophilic lithio-imidazoline in conjunction with nucleophilic alkylating agents (organometallics), i.e. a double umpolung of the inherent reactivity at C-2. The phenylthio group fitted this scheme, available both as an electrophile (in disulphides or sulphenyl chlorides) and as a nucleofugal leaving group. Thus the lithiated heterocycle from (4a) was reacted efficiently with phenyl disulphide[13] to produce the 2-phenylthio-2-imidazoline (6a)[6] (Scheme 1); the isolated yield of (6a) after aqueous work-up and chromatography was moderate (56%) but also isolated was 1-benzyl-2-imidazolidinone (7)

(25%),[6] presumed to arise by hydrolysis of the primary product during isolation. As this process must involve a substitution at C-2 by an oxygen nucleophile, it supported our original rationale for sulphenylation. Although (6a) was stable towards Grignard reagents, it did react with n-butyl-lithium (THF, -78°C) to afford 1-benzyl-2-butyl-2-imidazoline (8a)[6] in good yield (70%) (Scheme 1). The particular value of the arylthio group in this sequence was confirmed when (4a) was converted into the 2-butylthio derivative (6b)[6] (n-BuLi, THF, -78°C; Bu^nSSBu^n; 63%) with no observed hydrolysis to (7), and (6b) was inert towards n-butyl-lithium.[16]

To avoid losses of (6a) by hydrolysis and to create a 'direct' C-2 alkylation of 2-unsubstituted imidazolines, the sulphenylation and substitution were generally performed in 'one-pot'. Thus (4a) was treated successively with n-BuLi and phenyl disulphide (THF, -78°C), warmed to 0°C to complete sulphenylation, recooled to -78°C and treated with an alkyl-lithium. Conventional work-up and chromatography completes the sequence. In this way the 2-butyl-, 2-octyl-, and 2-phenyl-2-imidazolines (8a-c)[6] were prepared (Scheme 1) in 72, 76, and 52% yields, respectively, based on (4a). The 2-(2-furyl) derivative (8d)[6] was also prepared, albeit in poor yield in an unoptimised reaction.

Attempts to extend this sequence to secondary alkyl-lithiums produced unexpected findings. Treatment of the 2-phenylthio-2-imidazoline (6a) with s-BuLi (2 mol equiv., THF, -78°C) gave 1-benzyl-2-phenyl-2-imidazoline (9a ≡ 8c) (69%). Intrigued by this sulphur extrusion, we prepared the 2-(4-methylphenyl)thio-imidazoline (6c)[6] from (4) [BuLi, THF, -78°C; (4-methylphenyl)disulphide] in 55% yield; some urea (7) (21%) was again isolated. Desulphurisation of (6c) (2 mol equiv. s-BuLi, THF -78°C) gave 1-benzyl-2-(4-methylphenyl)-2-imidazoline (9b)[6] (46%). The orientation of the aryl ring was easily confirmed by the presence of signals for a 1,4-disubstituted benzene in the ^1H n.m.r. spectrum (δ 7.3 & 7.5, each 2H, d). This regiospecific sulphide contraction prompts us to suggest the mechanism of Scheme 2. Single electron transfer to the aryl ring from the s-alkyl-lithium[17] leads to a radical anion that, in the absence of a proton source, rearranges to an episulphide[18] bearing the negative charge on nitrogen. Further reduction and rearomatisation affords an N,S-dianion that can be postulated to undergo protonation and elimination of H_2S during work-up.



Scheme 2

We have thus demonstrated that a 2-metallo-2-imidazoline (2) may be alkylated (*via* sulphenylation-substitution) or arylated (*via* sulphur extrusion). The 2-substituted imidazolines (8) & (9) may be cleaved as we have reported earlier to complete a single carbon transfer and yield carboxylic acids[2c] or ketones.[3b] We thank Dr. M. Cox for helpful discussions, and ICI Pharmaceuticals and SERC for a CASE studentship (to J.R.N.).

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6. All new compounds gave spectral data (i.r., u.v., n.m.r., m.s.) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. Selected data: (**4a**): m.p. 46°C, b.p. 120°C at 2 mmHg; $\nu_{max.}$ (film) 1600 cm^{-1}; δ_H ($CDCl_3$) 3.1 and 3.8 (each 2H, t, NCH_2CH_2N), 4.25 (2H, s, CH_2Ph), 6.9 (1H, s, C2-*H*), and 7.3 (5H, s, Ar*H*); δ_C ($CDCl_3$) 157.2 (*C*-2), 137.2, 128.6, 127.7, 127.4, 55.2, 51.5, and 48.1. (**4b**): b.p. 160°C at 2.5 mmHg. (**4c**): b.p. 84°C at 0.5 mmHg. (**5b**): δ_H ($CDCl_3$) 2.0 (3H, s, C2-*Me*). (**5c**): δ_H ($CDCl_3$) 1.2 (3H, t, *J* 7.5 Hz, CH_2Me) and 2.24 (2H, q, *J* 7.5 Hz, CH_2Me). (**6a**): $\nu_{max.}$ (film) 1560 cm^{-1}; δ_H ($CDCl_3$) 3.25 and 3.7 (each 2H, m, NCH_2CH_2N), 4.35 (2H, s, CH_2Ph), 7.3 and 7.6 (8H and 2H, each m, Ar*H*); δ_C ($CDCl_3$) 162.7 (*C*-2), 136.5, 133.4, 128.4, 128.1, 128.0, 127.1, 126.9, 52.9, 51.0, and 50.0. (**6b**): δ_H ($CDCl_3$) 0.9 (3H, t, *Me*), 1.55 [4H, m, $(CH_2)_2Me$], and 3.2 (4H, m, NCH_2CH_2N and CH_2S). (**6c**): δ_H ($CDCl_3$) 7.1 and 7.45 (each 2H, d, Ar*H*) and 2.3 (3H, s, Ar*Me*). (**7**): m.p. 180°C; $\nu_{max.}$ (KBr) 1720 cm^{-1}; δ_H ($CDCl_3$) 3.4 (4H, m, NCH_2CH_2N), 4.45 (2H, s, CH_2Ph), 6.1 (1H, br s, N*H*), and 7.4 (5H, m, Ar*H*); δ_C ($CDCl_3$) 162.9 (*C*-2). (**8a**): $\nu_{max.}$ (film) 1610 cm^{-1}; δ_H ($CDCl_3$) 0.9 (3H, t, *Me*), 1.5 [4H, m, $(CH_2)_2Me$], and 2.3 (2H, t, C2-CH_2). (**8b**): δ_H ($CDCl_3$) 0.9 (3H, t, *Me*), 1.3 [12H, m, $(CH_2)_6Me$], and 2.3 (2H, t, C2-CH_2). (**8c**): m.p. 64-65°C; δ_H ($CDCl_3$) 7.4 and 7.7 (8H and 2H, each m, Ar*H*). (**9b**): δ_H ($CDCl_3$) 7.3 and 7.5 (each 2H, d, Ar*H*) and 2.35 (3H, s, Ar*Me*).
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