SYNTHESIS OF 4,5-DIHYDRO-1H-IMIDAZOLES FROM 1,5-DIHYDRO-2H-IMIDAZOLES USING 'NICKEL BORIDE'

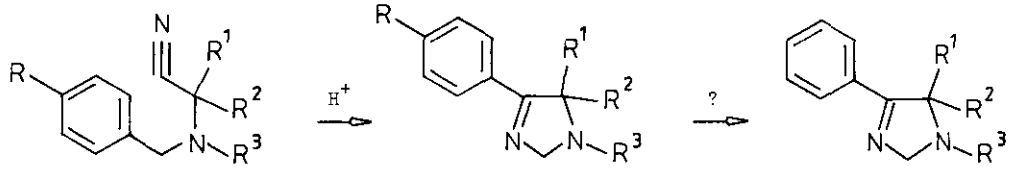
Melvin R. Euerby,[a] Amanda C. Oldroyd,[b] and Roger D. Waigh[b*]

[a] Department of Pharmaceutical Chemistry, School of Pharmacy, University of London, 29-39 Brunwick Square, London, WC1N 1AX, England

[b] Department of Pharmacy, University of Manchester, Manchester, M13 9PL, England

Abstract - In situ prepared 'nickel boride' generated from sodium borohydride and nickel (II) chloride cleanly transforms 1,5-dihydro-2H-imidazoles into 4,5-dihydro-1H-imidazoles in high yields by a double bond migration.

Research into the use of methylthio substituents as removable activating groups in the synthesis of N-heterocycles[1,2] prompted their application to the synthesis of 1,5-dihydro-2H-imidazoles (2) by the cyclisation of the methylthio activated benzylaminonitriles (1)[3] (Scheme 1). In the absence of the methylthio activating group, cyclisation fails to occur,[3] but it was anticipated that the unsubstituted 4-phenyl-1,5-dihydro-2H-imidazole (3) could be obtained by removal of the methylthio group from (2). This could be effected by reductive desulphurisation using 'nickel boride' generated by the action of sodium borohydride on nickel (II) chloride in situ, a method which we have shown to be superior in many respects to Raney nickel.[4]

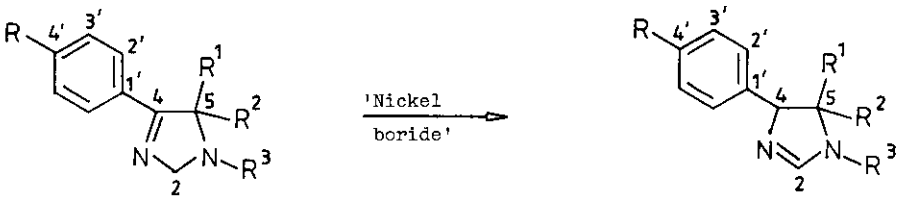


(1) (2) (3)

(Scheme 1, R = MeS)

As expected, the methylthio substituted 1,5-dihydro-2H-imidazoles (2a and b), when treated with 'nickel boride', underwent reductive desulphurisation of the thioether bond; unexpectedly, migration of the dihydroimidazole double bond occurred yielding the corresponding 4,5-dihydro-1H-imidazoles (4a and b) which are of potential pharmacological interest.[5] As a corollary the

analogous methoxy substituted 1,5-dihydro-2H-imidazoles (2c and d) were treated with 'nickel boride'. In these reactions double bond migration occurred yielding the corresponding methoxy substituted 4,5-dihydro-1H-imidazoles (4c and d). (Scheme 2).



(2a - d)

	R	R^1	R^2	R^3
a	MeS	$(CH_2)_5$		H
b	MeS	Me	Me	Me
c	MeO	$(CH_2)_5$		H
d	MeO	$(CH_2)_5$		Me

(4a - d)

	R	R^1	R^2	R^3
a	H	$(CH_2)_5$		H
b	H	Me	Me	Me
c	MeO	$(CH_2)_5$		H
d	MeO	$(CH_2)_5$		Me

(Scheme 2)

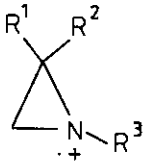
The structure of the 4,5-dihydro-1H-imidazoles (4) was unambiguously confirmed by the use of ^1H and ^{13}C n.m.r. and mass spectroscopy. The ^1H n.m.r. spectra of the 4,5-dihydro-1H-imidazoles (4) exhibited characteristic features including resonances in the region of δ_H 7.22 - 6.97 and 4.82 - 4.49 for the amidine and methine protons at positions 2 and 4 respectively; in comparison, the 1,5-dihydro-2H-imidazoles (2) possessed resonances in the region of δ_H 4.79 - 4.58 for the methylene protons at position 2.[3,6] Off resonance ^{13}C n.m.r. spectroscopy easily distinguished between the 1,5-dihydro-2H-imidazoles (2) and the 4,5-dihydro-1H-imidazoles (4) (Table 1): the former exhibited singlets and triplets in the region of δ_C 176.5 - 175.7 and 82.1 - 73.9 for the carbons in positions 4 and 2 respectively, whereas the latter possessed two doublets in the region of δ_C 78.5 - 73.5 and 156.7 - 152.2 for the carbons in the same positions. Carbon assignments (Table 1) were completed using the D.E.P.T. technique.

The plane of symmetry in the 1,5-dihydro-2H-imidazoles (2) is absent in the 4,5-dihydro-1H-imidazoles (4) and as a consequence the R^1 and R^2 substituents in the latter are non-equivalent. This difference in symmetry is observable in both the ^1H and ^{13}C n.m.r. spectra.

The fragmentation pattern in the mass spectra is also diagnostic in that the base peaks from the 1,5-dihydro-2H-imidazoles (2) correspond to the aziridinium ion (5),[3,6] whereas the base peaks for the 4,5-dihydro-1H-imidazoles (4) correspond to the iminium ion (6).

Table 1: ^{13}C N.m.r. spectra of the dihydroimidazoles (2a - d and 4a - d), (Solvent $CDCl_3$).

Compound	R	R^1	R^2	R^3	C-2	C-4	C-5	C-1'	C-2'	C-3'	C-4'
2a	14.5 (q)	32.5 25.0	25.0 (3 x t)	-	73.9 (t)	176.0 (s)	71.0 (s)	129.6 (s)	124.9 (d)	127.7 (d)	140.2 (s)
2b	14.7 (q)	20.5 (q)	20.5 (q)	30.7 (q)	79.4 (t)	176.1 (s)	67.0 (s)	129.1 (s)	125.0 (d)	127.4 (d)	140.9 (s)
2c	54.8 (q)	33.0 22.6	25.2 (3 x t)	-	73.9 (t)	175.7 (s)	71.3 (s)	125.4 (s)	113.0 (d)	128.7 (d)	160.0 (s)
2d	55.0 (q)	38.1 22.7	25.5 (3 x t)	29.6 (q)	82.1 (t)	176.5 (s)	74.0 (s)	127.0 (s)	113.5 (d)	129.2 (d)	160.5 (s)
4a	-	39.4 25.1 22.6	33.5 22.6 (5 x t)	-	153.5 (d)	73.5 (d)	68.0 (s)	138.2 (s)	127.9 (d)	127.3 (d)	127.3 (d)
4b	-	26.0 (q)	19.8 (q)	28.2 (q)	156.7 (d)	78.3 (d)	65.3 (s)	139.0 (s)	127.0 (d)	127.3 (d)	125.1 (d)
4c	55.1 (q)	39.4 25.5 22.7	33.8 23.0 (5 x t)	-	152.2 (d)	78.3 (d)	68.3 (s)	131.5 (s)	113.5 (d)	128.5 (d)	159.0 (s)
4d	55.1 (q)	32.6 25.1 21.8	29.3 22.9 (5 x t)	27.8 (q)	155.7 (d)	77.6 (d)	65.7 (s)	131.6 (s)	113.2 (d)	129.7 (d)	158.8 (s)



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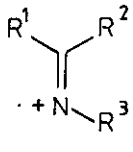
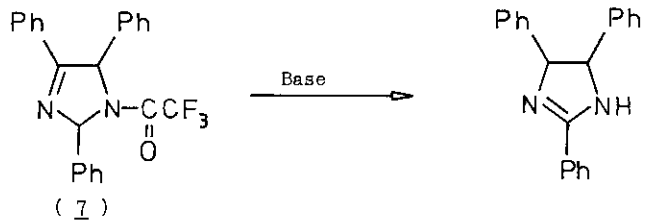


(6)

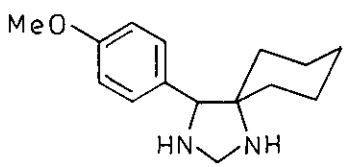
Double bond migration involving conversion of a 1,5-dihydro-2H-imidazole to a 4,5-dihydro-1H-imidazole was observed[7] when the 1,5-dihydro-1H-imidazole (7) was treated with base (Scheme 3).



(7)

(Scheme 3)

However, in our hands the 1,5-dihydro-2H-imidazole (2a) was inert to the effects of base treatment and also to nickel (II) chloride alone. In contrast, exposure of the 1,5-dihydro-2H-imidazole (2c) to sodium borohydride yielded the corresponding 1,3,4,5-tetrahydro-2H-imidazole (8) via reduction of the imine, suggesting that it is 'nickel boride' which is responsible for the double bond migration of 1,5-dihydro-2H-imidazoles (2) yielding 4,5-dihydro-1H-imidazoles (4).



(8)

Research is currently being undertaken to elucidate the mechanism, applicability and scope of this reaction.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage apparatus and are corrected. I.r. spectra were recorded with a Pye-Unicam SP3-100 instrument for potassium bromide discs or liquid films. ^{1}H and ^{13}C n.m.r. spectra, unless otherwise stated, were recorded on a Bruker WP80 spectrometer operating at 80 and 20.1 MHz respectively. M.s. data were obtained using an A.E.I. M530 spectrometer using electron ionisation unless otherwise stated. Microanalysis was carried out on a Perkin-Elmer 240 CHN analyser. The methylthio and methoxy substituted 1,5-dihydro-2H-imidazoles (2a - d) were

prepared as described in the literature.[3,6]

General Reaction

The 1,5-dihydro-2H-imidazole (2, 2mmol) and nickel (II) chloride hexahydrate (12mmol) were dissolved in methanol (20ml) and sodium borohydride (60mmol) added portionwise over a period of 30 min to the ice-cold mixture. Evolution of hydrogen and a black precipitate were observed on addition of sodium borohydride. When the addition was complete, the ice-bath was removed and stirring continued for 16 - 18 h at room temperature. To the ice-cooled reaction mixture was added hydrochloric acid (32% $^{w}/_{w}$, 40ml) and stirring continued for 10 min. Then ammonia solution (s.g. 0.88, 60ml) was added slowly to basify the mixture. The reaction mixture was filtered through a bed of 'celite', the filter cake washed with chloroform (3 x 25ml) and this chloroform used to extract the product from the aqueous filtrate. The combined chloroform extracts were washed with brine (1 x 25ml), dried with magnesium sulphate and evaporated to yield the 4,5-dihydro-1H-imidazoles (4a - d). The 4,5-dihydro-1H-imidazoles could be purified by column chromatography using basic (grade 1) alumina eluting with varying proportions of chloroform and methanol or by crystallisation from chloroform - petroleum (60-80°C).

Table 2: Analytical data for the 4,5-dihydro-1H-imidazoles (4a - d).

Compound	Yield[1]	mp °C	Solvent	Found % C	H	N	Required % C	H	N
4a	92(57)	152-155	$CHCl_3$-petroleum 60-80°C	78.2	8.4	13.0	78.5	8.5	13.1
4b	93(60)	125-127[2]	EtOH-di-iso-propyl ether	60.5	6.7	10.0	60.4	6.5	10.1
4c	96(75)	142-144	$CHCl_3$-petroleum 60-80°C	73.8	8.2	11.2	73.8	8.2	11.5
4d	85(67)	oil[3]							

[1] Crude yields calculated from n.m.r. data, values in parenthesis are purified non-optimised yields

[2] Hemioxalate salt

[3] Salt forms too hygroscopic for analysis

Table 3: ^{1}H N.m.r. and i.r. data for the 4,5-dihydro-1H-imidazoles (4a - d).

Compound	ν max/cm^{-1} C = N	^{1}H N.m.r. (δ values in p.p.m. Solvent $CDCl_3$)
4a	1590	[1] 7.27(5H,s,ArH), 7.21(1H,s,N=CH-N), 4.49(1H,s,ArCHN), 4.28(1H,s, NH exchangeable), 1.84-0.40(10H,m,5xCH_2).
4b	1590	[1] 7.27(5H,s,ArH), 7.11(1H,d,J=2Hz,N=CH-N), 4.76(1H,d,J=2Hz,ArCHN), 2.78(3H,s,CH_3N), 1.37(3H,s,CH_3C), 0.62(3H,s,CH_3C).
4c	1585	7.33(1H,s,N=CH-N), 7.16(2H,d,J=8.5Hz,ArH), 6.85(2H,d,J=8.5Hz, ArH), 4.44(1H,s,ArCHN), 3.80(3H,s,CH_3O), 2.86(1H,s,NH exchangeable), 1.92-0.67(10H,m,5xCH_2).
4d	1590	7.13(2H,d,J=8.5Hz,ArH), 6.97(1H,s,N=CH-N), 6.81(2H,d,J=8.5Hz, ArH), 4.82(1H,s,ArCHN), 3.80(3H,s,CH_3O), 2.78(3H,s,CH_3N), 1.89-0.65(10H,m,5xCH_2).

[1] 60 MHz Perkin-Elmer R12B

Table 4: Mass spectral fragmentation of the 4,5-dihydro-1H-imidazoles (4a - d).

Compound	Principal fragments, m/z (rel. intensity %)
4a	m/z 214(M^+,44%), 132(12), 120(18), 106(68), 98(92), 83(100), 79(11), 67(10), 47(14), 30(5).
4b	m/z 188(M^+,20%), 173(2), 117(7), 90(8), 72(100), 56(5), 45(14), 29(3).
4c	m/z 244(M^+,33%), 136(60), 121(17), 109(57), 98(72), 67(56), 40(100).
4d	m/z 258(M^+,45%), 136(11), 121(24), 112(100), 91(16), 86(30), 81(22), 77(20), 68(25), 55(28), 44(100), 40(93).

Sodium borohydride reduction of 1,5-dihydro-2H-imidazole (1c)

The general method was followed with the exception that nickel (II) chloride hexahydrate was omitted. 1,3,4,5-Tetrahydro-2H-imidazole (8) was formed as a mobile brown oil which, after purification by column chromatography on silica gel 60 (Merck 70-230 mesh) eluting with varying proportions of methanol in ethyl acetate, gave a golden oil (79%), δ_H ($CDCl_3$) 7.16 and 6.84(2 x 2H, 2 x d, J=8.5Hz, AA'XX', ArH), 4.18 and 3.97(2H, 2 x d, J=9Hz, NCH_2N), 3.82(4H, s, CH_3O and CHN), 1.82(2H, s, NH x 2 exchangeable), 1.85-0.47(10H, m, CH_2 x 5); δ_C ($CDCl_3$) 158.7(C-4',s) , 133.0 (C-1',s), 128.6(C-3',d), 113.4(C-2',d), 70.8(C-4,d), 63.8(C-5,s), 62.2(C-2,t), 55.0(CH_3O,q), 36.2, 33.0, 25.8, 23.2, 22.5(CH_2x5); m/z (chemical ionisation, isobutane), 247(M^+,14%), 235(28), 218

(60), 148(7), 136(8), 98(100), 94(17), 81(5), 57(7). The picrate had m.p. 217-220°C (decomp.) (From EtOH-diethyl ether) (Found: C,46.0; H,4.3; N,15.9. $C_{27}H_{28}N_8O_{15}$ requires C,46.0; H,4.0; N,15.9%).

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