Nucleophilic Addition to 4,5-Dihydroimidazoles: A Ketone Synthesis *via* Tetrahydrofolate Coenzyme Models

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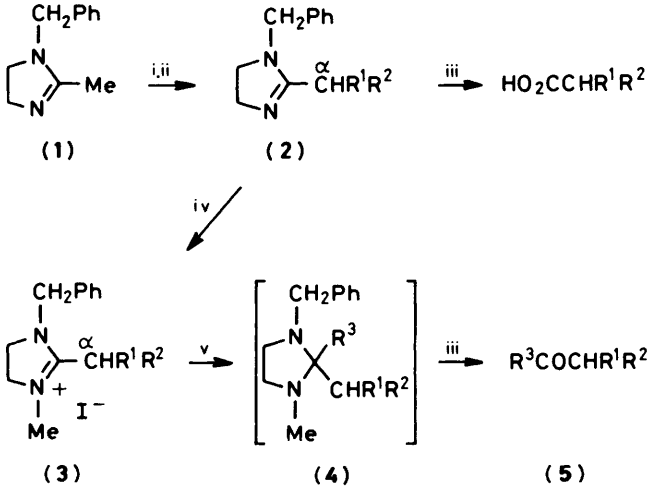
1-Benzyl-2-alkyl-3-methyl-4,5-dihydroimidazolium salts with Grignard reagents give addition products that are hydrolysed to ketones; 4,5-dihydroimidazoles and 4,5-dihydroimidazolium salts with hydride reagents afford *N*-alkylated ethane-1,2-diamines.

The coenzyme N^5,N^{10}-methenyltetrahydrofolate uses a 4,5-dihydroimidazole ring in the transfer of functionalised carbon at the carboxylate oxidation level.[1] Our recent report[2] of metallation and *C*-alkylation of 1-benzyl-2-methyl-4,5-dihydroimidazole (**1**) followed by hydrolysis of the products (**2**) (Scheme) mimics this process. As part of a continuing programme to develop synthetic methods patterned on the biological processes involving dihydroimidazoles, we have sought to extend this analogy to the reduced coenzyme N^5,N^{10}-methylenetetrahydrofolate and the carbonyl oxidation level, and have examined the potential of dihydroimidazoles as precursors to ketones and aldehydes. We detail here the results from reactions of 1-benzyl-2-alkyl-4,5-dihydroimidazoles with various carbon and hydrogen nucleophiles,[3,4] and the use of the former in a ketone synthesis.

Results and Discussion

1-Benzyl-2-alkyl-4,5-dihydroimidazoles (**2**) were recovered unchanged when treated with Grignard reagents, but use of the iminium species (**3**) afforded contrasting results (Scheme). The



Scheme. *Reagents:* i, Bu^nLi, R^1X; ii, Bu^nLi, R^2X; iii, H_3O^+; iv, MeI; v, R^3M

more reactive methiodide salts (**3**) were simply prepared from the dihydroimidazoles (**2**) in quantitative yield by reaction at 25 °C with excess of iodomethane. The salts in tetrahydrofuran (THF) were added to a Grignard reagent (3 mol equiv.) in THF and the mixture was heated at reflux for 3 h, during which time a reaction took place, presumed to be addition to produce the 2,2-disubstituted tetrahydroimidazoles (**4**). The intermediate was not isolated but decomposed on mild acidic work-up (2M hydrochloric acid at 0 °C) such that the ketones (**5**) were obtained in good overall yield from the dihydroimidazoles (**2**) on simple extraction with diethyl ether (Table 1, entries 1—6).

Table 1. Synthesis of ketones (**5**) from salts (**3**) and R^3M

Entry	R^1	R^2	R^3	M	Yield (%)[a]
1	H	$[CH_2]_7Me$	Me	MgBr	85
2	H	$[CH_2]_7Me$	$[CH_2]_3Me$	MgBr	70
3	H	$[CH_2]_3Me$	Me	MgBr	55
4	H	$[CH_2]_3Me$	$[CH_2]_3Me$	MgBr	64
5	Me	$[CH_2]_7Me$	Me	MgBr	83
6	Me	$[CH_2]_7Me$	$[CH_2]_3Me$	MgBr	56
7	H	$[CH_2]_7Me$	$[CH_2]_3Me$	Li	80
8	Me	$[CH_2]_7Me$	$[CH_2]_3Me$	Li	68

[a] Not optimised; based on dihydroimidazole (**2**).

This new ketone synthesis, whilst accommodating branching at the dihydroimidazole α-carbon (entries 5,6), is sensitive to the structure of the Grignard reagent used. Satisfactory results were obtained with primary organomagnesium halides but secondary (*e.g.*, isopropylmagnesium bromide) and aryl (*e.g.*, phenylmagnesium bromide) ones add slowly to give low yields. It is probable that α-deprotonation of salts (**3**) (with regeneration of the salt on work-up) and/or *N*-dealkylation intervene in these cases; indeed some 1-benzyl-2-nonyl-4,5-dihydroimidazole (**2**; R^1 = H, R^2 = $[CH_2]_7Me$) was isolated from the reaction of the corresponding methiodide (**3**; R^1 = H, R^2 = $[CH_2]_7Me$) with phenylmagnesium bromide, along with recovered quaternary salt and some 1-phenyldecan-1-one.

We have found that an alkyl-lithium will also add to the dihydroimidazolium iodides (**3**). An exothermic reaction ensues on treatment of a compound (**3**) in THF at 25 °C with butyllithium (3 mol equiv.) and, after 3 h, work-up as above led to ketones in yields superior (Table 1, entries 7,8) to those obtained from the corresponding reactions with butylmagnesium bromide (entries 2,6). It is possible that the more reactive organolithiums can be used in cases where Grignard addition is unsatisfactory.

In combination with the α-metallation/*C*-alkylation of 4,5-dihydroimidazoles,[2] this new ketone synthesis completes transfer of a two-carbon unit from 1-benzyl-2-methyl-4,5-dihydroimidazole (**1**), synthetically equivalent to acetic acid, into the carbonyl and α-carbon atoms of a ketone.

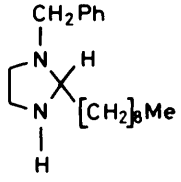
In an attempt to produce tetrahydroimidazoles that would act as aldehyde precursors, we have examined the reactions of some hydrogen nucleophiles with dihydroimidazoles. When the salt (**3**; R^1 = H, R^2 = $[CH_2]_7Me$) was treated with sodium

Table 2. Reduction of the dihydroimidazole (2; R^1 = H, R^2 = $[CH_2]_7Me$) with $LiAlH_4$–Et_2O

T (°C)	Reaction time (h)	Components of reaction mixture (%) (2)	(6)	(7)
−78	3 h	100	—	—
−40	3 h	100	—	—
−20	1.5 h	100	—	—
−20	2 h	90	8	2
−20	2.5 h	85	10	5
−20	3 h	80	10	10
−10	0.5 h	95	5	—
−10	1 h	85	10	5
−10	1.5 h	80	10	10
−10	2 h	40	10	50
−10	2.5 h	30	10	60
−10	3 h	25	10	65
25	3 h	—	10	90

borohydride (EtOH; 25 or −78 °C), potassium borohydride (EtOH; 25 °C), or tetrabutylammonium borohydride (CH_2Cl_2; −78 to 0 °C) over-reduction to an *N,N,N'*-trialkylethane-1,2-diamine {identified as $Me[CH_2]_9NMe[CH_2]_2NHCH_2Ph$ or $Me[CH_2]_9N(CH_2Ph)[CH_2]_2NHMe$} was observed. The desired tetrahydroimidazole (4; R^1 = R^3 = H, R^2 = $[CH_2]_7Me$), an authentic sample of which was prepared for comparison, was not observed during any of these experiments. It would appear that, even at low temperature, as tetrahydroimidazole is formed it is consumed at a comparable rate. In contrast the methiodide salt was unaffected by sodium cyanoborohydride under various conditions, including in acidic solution.

Reduction of the less reactive unquaternised dihydroimidazole (2; R^1 = H, R^2 = $[CH_2]_7Me$) with lithium aluminium hydride in Et_2O at various temperatures was examined in detail, and the results are summarised in Table 2. At very low temperatures no reaction was detected after 3 h. Reduction was observed at −20 °C and above, and monitoring by g.l.c. demonstrated the initial appearance of the tetrahydroimidazole (6), identified by comparison with an independently prepared



(6)

sample, which never accumulated but was consumed to produce the alkylated ethane-1,2-diamine $Me[CH_2]_9NH[CH_2]_2NHCH_2Ph$ (7), *i.e.* over-reduction, before substantial conversion of the dihydroimidazole had taken place. The proportion of the intermediate (6) present was substantiated by isolation of the corresponding yield of decanal upon aqueous acidic work-up, after 3 h, of the reactions mixtures obtained at −20, −10, and 25 °C. Complete over-reduction was observed after at least 30 min at reflux. Reduction of (2; R^1 = H, R^2 = $[CH_2]_7Me$) with sodium borohydride (EtOH; 25 °C) was slower, requiring in excess of 72 h for complete over-reduction, but behaved similarly. Lithium borohydride (THF; 25 °C), sodium cyanoborohydride (MeOH; 25 °C; or aqueous THF, pH 3), and lithium tri-t-butoxyaluminium hydride (Et_2O; 25 °C) in contrast did not reduce the dihydroimidazole, whilst sodium–ammonia reduction produced merely *N*-debenzylation as expected.[2] Neither compounds (2) nor (3) were affected by aluminium amalgam[5] or catalytic hydrogenation. A plausible pathway for the observed reduction of tetrahydroimidazoles to diamines proceeds *via* ring-opening to an amino imine, followed by reduction of the carbon–nitrogen double bond.[4]

1-Benzyl-2-alkyl-4,5-dihydroimidazoles, as tetrahydrofolate coenzyme models, are thus not yet available as aldehyde precursors but can be used to synthesise ketones and unsymmetrically alkylated ethane-1,2-diamines. The ketone synthesis is comparable in efficiency to analogous approaches involving dihydro-oxazoles and dihydro-oxazines;[6] the limitations we have found are also evident in these methods.

Experimental

General directions are as in our earlier publication.[7] Gas–liquid chromatography (g.l.c.) was performed on a glass column packed with 5% KOH-washed 10% Carbowax 20M, at an oven temperature of 250 °C.

1-Benzyl-3-methyl-2-nonyl-4,5-dihydroimidazolium Iodide (3; R^1 = H, R^2 = $[CH_2]_7Me$).—1-Benzyl-2-nonyl-4,5-dihydroimidazole[2] (2; R^1 = H, R^2 = $[CH_2]_7Me$) (1.84 g, 6.4 mmol) was treated dropwise with iodomethane (1.35 g, 9.5 mmol) and the resulting mixture was stirred at 25 °C for 0.5 h. Concentration under reduced pressure afforded a quantitative yield of the title dihydroimidazolium iodide as a thick oil; δ 0.9 (3 H, t, Me), 1.3 (12 H, m, 6 × CH_2), 1.6 (2 H, m, CH_2), 2.8 (2 H, t, CH_2), 3.3 (3 H, s, $\overset{+}{N}Me$), 4.0 (4 H, m, NCH_2CH_2N), 4.7 (2 H, s, CH_2Ph), and 7.4 (5 H, s, Ph). This material was not further characterised but was used directly.

1-Benzyl-3-methyl-2-pentyl-4,5-dihydroimidazolium iodide (3; R^1 = H, R^2 = $[CH_2]_3Me$) was prepared in the same way, from compound (2; R^1 = H, R^2 = $[CH_2]_3Me$),[2] and was used directly.

Synthesis of Ketones.—Undecan-2-one (5; R^1 = H, R^2 = $[CH_2]_7Me$, R^3 = Me). A solution of 1-benzyl-3-methyl-2-nonyl-4,5-dihydroimidazolium iodide (3; R^1 = H, R^2 = $[CH_2]_7Me$) (2.5 g, 5.9 mmol) in dry THF (25 ml) was added dropwise to a stirred solution of methylmagnesium bromide (2.1 g, 17.6 mmol) in THF (25 ml) under nitrogen. The reaction mixture was heated under reflux for 3 h, cooled to 0 °C, treated with hydrochloric acid (2M; 50 ml), and the resulting solution was stirred for 2 h at this temperature. The reaction mixture was then extracted with diethyl ether (3 × 50 ml), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford undecan-2-one (0.85 g, 85%), b.p. 116—120 °C at 13 mmHg (lit.,[8] 228 °C at 760 mmHg); semicarbazone m.p. 117—118 °C (lit.,[8] 122 °C); $\nu_{max.}$(film) 1 720 cm^{-1}; δ 0.9 (3 H, t, Me), 1.2 (12 H, br s, 6 × CH_2), 1.6 (2 H, m, CH_2), 2.2 (3 H, s, MeCO), and 2.5 (2 H, t, CH_2CO).

The following ketones were also prepared by this method from the appropriate dihydroimidazolium iodide (3) and Grignard reagent (see Table 1).

Tetradecan-5-one (5; R^1 = H, R^2 = $[CH_2]_7Me$, R^3 = $[CH_2]_3Me$), b.p. 85—88 °C at 0.7 mmHg (lit.,[9] 145—146 °C at 16 mmHg), m.p. 23 °C (lit.,[9] 22.6 °C); $\nu_{max.}$(film) 1 700 cm^{-1}; δ 0.9 (6 H, t, 2 × Me), 1.3 (14 H, br s, 7 × CH_2), 1.6 (4 H, m, 2 × CH_2), and 2.5 (4 H, t, 2 × CH_2CO).

Heptan-2-one (5; R^1 = H, R^2 = $[CH_2]_3Me$, R^3 = Me), b.p. 150—154 °C (lit.,[10] 151 °C); $\nu_{max.}$(film) 1 720 cm^{-1}; δ 0.9 (3 H, t, Me), 1.3 (4 H, m, 2 × CH_2), 1.6 (2 H, m, CH_2), 2.2 (3 H, s, MeCO), and 2.5 (2 H, t, CH_2CO).

Decan-5-one (5; R^1 = H, R^2 = R^3 = $[CH_2]_3Me$), b.p. 195—

200 °C (lit.,[11] 204 °C); $\nu_{max.}$(film) 1 710 cm^{-1}; δ 0.9 (6 H, t, 2 × Me), 1.3 (6 H, m, 3 × CH_2), 1.6 (4 H, m, 2 × CH_2), and 2.4 (4 H, t, 2 × CH_2CO).

3-Methylundecan-2-one (**5**; $R^1 = R^3 = Me$, $R^2 = [CH_2]_7Me$) (Found: M^+, 184.180. $C_{12}H_{24}O$ requires M, 184.183), *semicarbazone* m.p. 102—104 °C (from aqueous ethanol) (Found: C, 63.8; H, 11.05; N, 17.5. $C_{13}H_{27}N_3O \cdot 0.2H_2O$ requires C, 63.75; H, 11.25; N, 17.15%); $\nu_{max.}$(film) 1 705 cm^{-1}; δ 0.9 (3 H, t, Me), 1.1 (3 H, d, Me), 1.3 (12 H, br s, 6 × CH_2), 1.6 (2 H, m, CH_2), 2.2 (3 H, s, MeCO), and 2.5 (1 H, m, CHCO).

6-Methyltetradecan-5-one (**5**; $R^1 = Me$, $R^2 = [CH_2]_7Me$, $R^3 = [CH_2]_3Me$), an oil after Kugelrohr distillation (oven temperature 120 °C) at 0.5 mmHg (Found: M^+, 226.229. $C_{15}H_{30}O$ requires M, 226.230), pure by t.l.c. (SiO_2; diethyl ether); $\nu_{max.}$(film) 1 705 cm^{-1}; δ 0.9 (6 H, 2 × Me), 1.0 (3 H, d, Me), 1.3 (14 H, br s, 7 × CH_2), 1.6 (4 H, m, 2 × CH_2), and 2.4 (3 H, m, CH_2CO and CHCO).

Tetradecan-5-one was also prepared by the following alternative procedure. To a solution of 1-benzyl-3-methyl-2-nonyl-4,5-dihydroimidazolium iodide (**3**; $R^1 = H$, $R^2 = [CH_2]_7Me$) (2 g, 4.7 mmol) in dry THF (25 ml) stirred under nitrogen at 25 °C was added butyl-lithium (11 ml of a 1.29M solution in hexane; 14.2 mmol) during 15 min, and the mixture was stirred for 3 h at 25 °C. After being cooled to 0 °C the solution was then treated with hydrochloric acid (2M; 50 ml), stirred for 2 h at this temperature, and extracted with diethyl ether (3 × 50 ml). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford tetradecan-5-one (1.6 g, 80%), identical with material prepared using a Grignard reagent (see earlier). The above procedure was also used to prepare 6-methyltetradecan-5-one from (**3**; $R^1 = Me$, $R^2 = [CH_2]_7Me$) (see Table 1).

Reduction of 1-Benzyl-3-methyl-2-nonyl-4,5-dihydroimidazolium Iodide (**3**; $R^1 = H$, $R^2 = [CH_2]_7Me$).—A solution of the dihydroimidazolium iodide (0.5 g, 1.16 mmol) in ethanol (50 ml) at 25 °C was treated with sodium borohydride (0.5 g, 13.2 mmol) added in portions. The mixture was stirred for 0.5 h and concentrated under reduced pressure to leave a residue, which was partitioned between chloroform (50 ml) and water (50 ml). The organic layer was dried ($MgSO_4$) and evaporated to afford N^1-*benzyl*-N^1-(or N^2)-*decyl*-N^2-*methylethane*-1,2-*diamine* (0.25 g, 80%) as an oil (Found: M^+, 304.288. $C_{20}H_{36}N_2$ requires M, 304.288), pure by g.l.c.; $\nu_{max.}$(film) 3 200, 2 900, 1 480, and 760 cm^{-1}; δ 0.9 (3 H, t, Me), 1.3 (17 H, br s, 8 × CH_2 and NH), 2.2 (3 H, s, NMe), 2.3 (2 H, m, CH_2), 2.4—2.8 (4 H, m, NCH_2CH_2N), 3.8 (2 H, s, CH_2Ph), and 7.2 (5 H, s, Ph); *m/z* 304 (M^+), 184 (100%), 134, 120, and 91.

1-Benzyl-3-methyl-2-nonyl-2,3,4,5-tetrahydroimidazole (**4**; $R^1 = R^3 = H$, $R^2 = [CH_2]_7Me$).—N^1-Benzyl-N^2-methylethane-1,2-diamine[12] (1.1 g, 6.7 mmol) and decanal (1.1 g, 7 mmol) were mixed, diluted with diethyl ether (100 ml), and treated with magnesium sulphate. After 16 h the suspension was filtered and the filtrate was concentrated under reduced pressure to leave a residue, which was subjected to Kugelrohr distillation (oven temperature 100—105 °C) at 0.5 mmHg to afford the *title tetrahydroimidazole* (1.8 g, 90%) as an oil (Found: M^+, 302.274. $C_{20}H_{34}N_2$ requires M, 302.272), pure by g.l.c.; $\nu_{max.}$(film) 2 900, 1 480, 750, and 700 cm^{-1}; δ 0.9 (3 H, t, Me), 1.3 (14 H, br s, 7 × CH_2), 1.5 (2 H, m, CH_2), 2.35 (3 H, s, NMe), 2.4 (1 H, m, CH), 2.8—3.1 (4 H, m, NCH_2CH_2N), 3.3 and 3.9 (each 1 H, d, *J* 6 Hz, CH_2Ph), and 7.3 (5 H, s, Ph); *m/z* 302 (M^+), 177, 176, 92 (100%), and 91.

1-Benzyl-2-nonyl-2,3,4,5-tetrahydroimidazole (**6**) was prepared as above from *N*-benzylethane-1,2-diamine[13] and decanal to give, after Kugelrohr distillation (oven temperature 100 °C) at 0.1 mmHg, an *oil* (94%) [Found: $(M - H)^+$, 287.248. $C_{19}H_{32}N_2$ requires $(M - H)$, 287.249), pure by g.l.c.; $\nu_{max.}$(film) 3 400, 2 900, 1 460, 740, and 700 cm^{-1}; δ 0.9 (3 H, t, Me), 1.4 (16 H, br s, 8 × CH_2), 2.2 (1 H, br s, NH), 2.4 (1 H, m, CH), 3.0 (4 H, m, NCH_2CH_2N), 3.4 and 4.0 (each 1 H, d, *J* 6 Hz, CH_2Ph), and 7.4 (5 H, s, Ph); *m/z* 287 ($M^+ - 1$), 170, 120, 92, and 91 (100%).

Reduction of 1-Benzyl-2-nonyl-4,5-dihydroimidazole (**2**; $R^1 = H$, $R^2 = [CH_2]_7Me$).—To a solution of the dihydroimidazole (10 g, 35 mmol) in dry diethyl ether (100 ml) at 25 °C was added portionwise lithium aluminium hydride (2.7 g, 71 mmol). The mixture was heated under reflux for 30 min, then cooled in ice and treated successively with water (3 ml), aqueous sodium hydroxide (2M; 3 ml), and water (10 ml). The resulting suspension was filtered, dried ($MgSO_4$), and concentrated under reduced pressure to afford N^1-*benzyl*-N^2-*decylethane*-1,2-*diamine* (9.8 g, 98%), b.p. 180—185 °C at 0.3 mmHg (Found: C, 78.5; H, 11.95; N, 9.35%; M^+, 290.272. $C_{19}H_{34}N_2$ requires C, 78.55; H, 11.8; N, 9.65%; M, 290.272); $\nu_{max.}$(film) 3 300, 2 900, 1 500, 1 480, 1 475, and 760 cm^{-1}; δ 0.9 (3 H, t, Me), 1.25 (16 H, br s, 8 × CH_2), 1.4 (2 H, s, 2 × NH), 2.5 (2 H, t, CH_2), 2.7 (4 H, m, NCH_2CH_2N), 3.8 (2 H, s, CH_2Ph), and 7.2 (5 H, s, Ph); *m/z* 290 (M^+), 171, 170 (100%), 120, and 91. This material was identical with a sample prepared by heating *N*-(2-chloroethyl)-benzylamine (7.1 g, 34 mmol) and decylamine (33% solution in ethanol; 220 ml, 0.46 mol) together at 50 °C for 16 h, followed by evaporation of solvent under reduced pressure and fractional distillation of the residue.

The reduction of the imidazole (**2**; $R^1 = H$, $R^2 = [CH_2]_7Me$) by lithium aluminium hydride was also studied at various temperatures (see Table 2) as follows. To a solution of the dihydroimidazole (1.85 g, 6.4 mmol) in dry diethyl ether (50 ml) stirred at the appropriate temperature was added lithium aluminium hydride (0.31 g, 8.15 mmol) during 5 min. Aliquots (2 ml) were taken at intervals (see Table 2), quenched with water (0.2 ml), diluted with diethyl ether, dried ($MgSO_4$), and concentrated under reduced pressure to leave a liquid residue, which was examined by g.l.c. After 3 h the remaining ethereal solution from reductions performed at −20, −10, or 25 °C was stirred at 25 °C for 30 min with hydrochloric acid (2M; 50 ml). The ethereal layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure to afford decanal (0.1 g, 10%), identical with authentic samples.

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