Nucleophilic Addition to 2-Imidazolines. A Ketone Synthesis *via* Tetrahydrofolate Coenzyme Models

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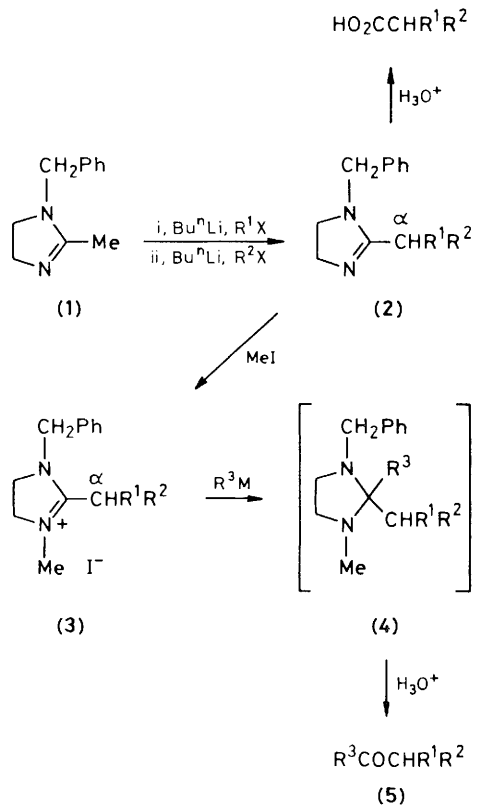
2-Alkyl-1-benzyl-3-methyl-2-imidazolinium salts with Grignard reagents give addition products that are hydrolysed to ketones; 2-imidazolines and 2-imidazolinium salts with hydride reagents afford *N*-alkylated 1,2-diaminoethanes.

The coenzyme N^5,N^{10}-methenyltetrahydrofolic acid uses a 2-imidazoline ring in the transfer of functionalised carbon at the carboxylate oxidation level.[1] Our recent report[2] of α-metallation and *C*-alkylation of 1-benzyl-2-methyl-2-imidazoline (**1**) followed by hydrolysis of the products (**2**) (Scheme 1) mimics these processes. In order to extend this analogy to the reduced coenzyme N^5,N^{10}-methylenetetrahydrofolate, we have examined the potential of imidazolines



Scheme 1

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

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

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

as precursors to ketones and aldehydes. We present here some relevant results from reactions of 2-imidazolines with carbon and hydrogen nucleophiles.

2-Alkyl-1-benzyl-2-imidazolines (**2**) were recovered unchanged when treated with Grignard reagents, but contrasting results were obtained by use of the iminium species (**3**) (Scheme 1). Imidazolines (**2**) were easily and quantitatively converted into the more reactive methiodides (**3**) by reaction with MeI (neat, 2 equiv., 1 h at 20 °C). These salts (**3**)† in tetrahydrofuran (THF) were added to a Grignard reagent (3 equiv.) in THF and the mixture heated under reflux for 3 h. A reaction took place, presumed to be addition to give the 2,2-disubstituted imidazolidines (**4**) which were not isolated. Acidic work-up (2 M HCl, 2 h at 0 °C) and ether extraction afforded the ketones (**5**)‡ in good overall yield from the imidazolines (**2**) (Table 1, entries 1—6).

This new ketone synthesis can accommodate branching at the imidazoline α-carbon (entries 5, 6) but is more sensitive to the structure of the Grignard reagent. Primary organomagnesium halides add satisfactorily to (**3**) but secondary (*e.g.* Pr^iMgBr) and aryl (*e.g.* PhMgBr) add slowly to give low yields; *N*-demethylation and/or α-deprotonation of (**3**) intervene in these cases.

We have observed that an alkyl-lithium will also add to imidazolinium iodides (**3**). Addition of Bu^nLi (3 equiv.) in hexane to salts (**3**) in THF at 20 °C gave an exothermic reaction. After 3 h at 20 °C, work-up as above led to ketones in improved yields (Table 1, entries 7, 8) over those observed in the corresponding reactions with Bu^nMgBr (entries 2, 6). It is likely that the more reactive organolithiums can be used in cases where Grignard reagents do not give satisfactory addition.

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

We have explored reactions of hydrogen nucleophiles with imidazolines in an attempt to produce imidazolidines that would act as aldehyde precursors. When the salt {(**3**); R^1 = H, R^2 = $[CH_2]_7Me$} was treated with $NaBH_4$ (EtOH, 25 °C or −78 °C), KBH_4 (EtOH, 25 °C), or $Bu^n_4NBH_4$ (CH_2Cl_2, 25 °C) over-reduction to an *N*,*N*′,*N*′-trialkyl-1,2-diaminoethane {$Me[CH_2]_9NMe[CH_2]_2NHCH_2Ph$ or $Me[CH_2]_9N(CH_2Ph)[CH_2]_2NHMe$‡} was observed; $NaBH_3CN$ did not reduce the salt under various conditions. The unquaternised imidazoline {(**2**); R^1 = H, R^2 = $[CH_2]_7Me$} reacted with $LiAlH_4$ at temperatures above −10 °C. Monitoring by g.l.c. demonstrated the initial appearance of an intermediate, presumably the imidazolidine, which never accumulated but was consumed to produce the alkylated 1,2-diaminoethane $Me[CH_2]_9NH[CH_2]_2NHCH_2Ph$,‡ *i.e.* over-reduction, before substantial conversion of imidazoline had taken place. $NaBH_4$ reduction (EtOH) was slower but behaved similarly. $LiBH_4$ (THF), $NaBH_3CN$ (THF, pH 3), and $LiAlH(OBu^t)_3$ all failed to react with the imidazoline, whilst Na–NH_3(l) afforded *N*-debenzylation.[3] Neither (**2**) nor (**3**) was affected by hydrogenation or Al–Hg. A different substituent at N-1 may be necessary to stop reduction at the imidazolidine stage.[4]

2-Alkyl-1-benzyl-2-imidazolines, as tetrahydrofolate coenzyme models, are thus not yet available as aldehyde precursors but can be used to synthesise ketones and unsymmetrically alkylated 1,2-diaminoethanes.

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† Methiodides (**3**) gave satisfactory ^1H n.m.r. spectra and were not generally further characterised.

‡ New compounds gave spectra consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. Ketones (**5**), where appropriate, had b.p. or semicarbazide m.p. in agreement with published values.