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A New Sequence for the C^{α}-Alkylation of 4,5-Dihydroimidazoles

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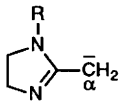
The *C*-alkylation of 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole with halogeno- and dihalogeno-alkanes is described; subsequent removal of the ethoxycarbonyl group provides a new route to 2-alkyl-4,5-dihydroimidazoles. 1,3-Dihalogenoalkanes afford imidazo-[1,2-*a*]pyridines.

An important part of our studies of the 4,5-dihydroimidazole (2-imidazoline) heterocycle, a moiety that occurs in a number of pharmacologically active molecules[1] and is involved in biological C_1-transfers as N^5,N^{10}-methenyltetrahydrofolate,[2] is the generation of nucleophilic reactivity at the α-carbon atom as in **1**.[3] We have previously indicated the value of the readily available and crystalline enamino ester **2**[3b] as a C-nucleophile in conjugate additions and annulations,[4] and now report the use of **2** in alkylation reactions as a substitute for lateral metallation of 1-benzyl-2-methyl-4,5-dihydroimidazole **3a**.[3a]



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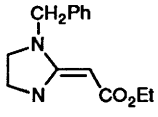

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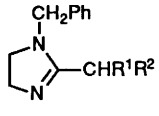
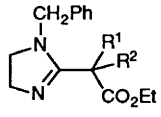
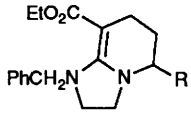


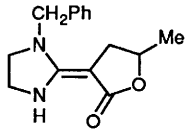
3 **a**; $R^1 = R^2 = H$
b; R^1 = Et, $R^2 = H$
c; R^1, $R^2 = -(CH_2)_4-$



4 **a**; $R^1 = (CH_2)_4Me$, $R^2 = H$
b; $R^1 = (CH_2)_3Me$, $R^2 = H$
c; R^1 = Et, $R^2 = H$
d; $R^1 = CH_2Ph$, $R^2 = H$
e; $R^1 = (CH_2)_3OSiMe_2Bu^t$, $R^2 = H$
f; $R^1 = R^2$ = Et
g; $R^1 = R^2 = CH_2Ph$
h; R^1, $R^2 = -(CH_2)_4-$
i; R^1, $R^2 = -(CH_2)_5-$



5 **a**; R = H
b; R = Me



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Initial studies exploited the enamine character of **2** that we had observed in conjugate additions.[4a] Treatment of the enamino ester **2** in ethanol with 1-iodopentane (Et_3N, 1 mol equiv., reflux 18 h) gave the *C*-alkylated product **4a**† in only 24% yield with substantial recovery of starting material, along with polar material presumed to be quaternised compounds, whereas heating **2** with 1-iodobutane in dimethylformamide (110 °C, 24 h) gave the alkylated dihydroimidazole **4b** in 67% yield.‡ A more generally useful procedure, however, involved stoichiometric deprotonation of **2** with sodium hydride [1 mol equiv., tetrahydrofuran (THF), 0 °C] before addition of the alkylating agent (1 mol equiv.) and either heating at reflux for 4 h or stirring at 20 °C overnight.[5] Using this method with iodoethane, benzyl bromide and 3-(*tert*-butyldimethylsilyloxy)-1-bromopropane, the alkylated dihydroimidazoles **4c–e** were obtained (see Table 1). All of the *C*-monoalkylation products **4a–e** were found to exist as the imine tautomer illustrated, rather than the enamine tautomer seen in **2**,[3b] as indicated by an absorption at approx. 1735 cm^{-1} in the IR spectrum (C=O, unconjugated ester) and an α-proton resonance in the ^1H NMR spectrum (typically δ 3.7).[4a] Use of 2 mol equiv. each of sodium hydride and of the halogenoalkanes iodoethane or benzyl bromide afforded the *C*-dialkylated imidazolines **4f,g**, respectively (Table 1). Attempts to produce unsymmetrically dialkylated compounds **4** ($R^1 \neq R^2 \neq H$) by a second separate alkylation of the monoalkylated materials using the same method have so far failed.

Table 1 Synthesis of *C*-alkylated 4,5-dihydroimidazoles **4** using the NaH–THF protocol[a]

Alkyl halide (mol equiv.)	Dihydroimidazole **4** (yield %)
EtI (1)	**4c** (71)
$PhCH_2Br$ (1)	**4d** (74)
$Bu^tMe_2SiO(CH_2)_3Br$ (1)	**4e** (36)
EtI (2.2)	**4f** (84)
$PhCH_2Br$ (2.2)	**4g** (79)
$Br(CH_2)_4Br$ (1)	**4h** (67)
$Br(CH_2)_5Br$ (1)	**4i** (35)

[a] Typical experimental directions (for **4c**). Sodium hydride (60% dispersion in oil; 0.04 g, 1 mmol) was added to a stirred solution of the tetrahydroimidazole **2** (0.246 g, 1 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min and then at 20 °C for 1 h; iodoethane (0.156 g, 1 mmol) was then added dropwise. The solution was stirred overnight and then poured into saturated aq. $NaHCO_3$ (20 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic phases were dried and evaporated under reduced pressure, and the residue was chromatographed on silica, eluting with ethyl acetate–hexane–triethylamine (15:4:1 v/v/v), to afford **4c** as a colourless oil.

Interesting results were observed using this protocol with dihalogenoalkanes as electrophiles. Treatment of the enamino ester **2** with 1,4-dibromobutane or 1,5-dibromopentane (1 mol equiv.) and sodium hydride (2.2 mol equiv.) led to the cyclic *C*-dialkylated imidazolines **4h,i** (see Table 1), whereas the 1,3-dihalides, 1,3-dibromopropane and 1,3-dibromobutane afforded instead the *C*,*N*-dialkylated products of annulation, the hexahydroimidazo[1,2-*a*]pyridines **5a** (64%) and **5b** (44%), respectively. Under the same conditions 1,2-dibromoethane gave only recovered starting material **2**.¶

Reaction of the enamino ester **2** with methyloxirane [BuLi (1 mol equiv.), THF, 0 °C→reflux, 2h] also gave *C*-alkylation

† All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
‡ Use of dimethyl sulphoxide at 130 °C led to an inseparable mixture.
¶ We thank Rachel Lloyd and Jeffrey W. Hobbs for this experiment.

which was followed by transesterification to afford the lactone **6** (31%).[6,†]

To confirm the equivalence of the enamino ester **2** to the α-deprotonated dihydroimidazole **1**, we completed the removal of the ethoxycarbonyl group. For example, hydrolysis decarboxylation of the monoethyl compound **4c** (1% HCl in MeOH–H_2O, reflux 3 days) afforded the 2-propyl-4,5-dihydroimidazole **3b** (74%); more vigorous conditions (2 mol dm^{-3} aq. HCl, reflux 10 days) were required for the α,α-dialkylated derivatives, *e.g.* to prepare the 2-cyclopentyl-4,5-dihydroimidazole **3c** (77%) from **4h**.[4a] Cyclic compounds of this type have not been available by the lateral metallation route.

We have therefore demonstrated the *C*-alkylation of enamino ester **2**, as an alternative route to α-alkylated dihydroimidazoles (and hence to alkanoic acids[3a] and ketones[7]), and in a new route to imidazo[1,2-*a*]pyridines.

Acknowledgements

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† A similar reaction with phenyloxirane was indicated by ^1H NMR spectroscopy although the product awaits full characterisation.

References

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6 For related lactones, see: R. C. F. Jones and S. C. Hirst, *Tetrahedron Lett.*, 1989, **30**, 5365.
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