

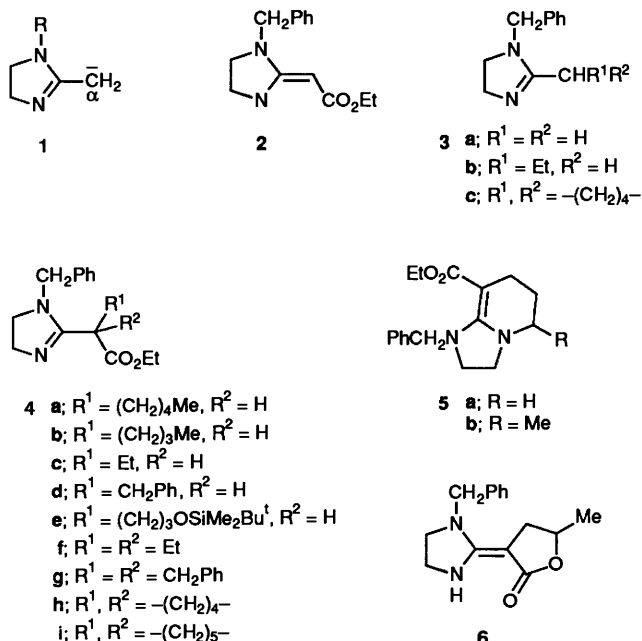
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A New Sequence for the C^α-Alkylation of 4,5-Dihydroimidazoles

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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 molecules¹ and is involved in biological C₁-transfers as N⁵,N¹⁰-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}



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 (Et₃N, 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

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 ₂ Br (1)	4d (74)
Bu ^t Me ₂ SiO(CH ₂) ₃ Br (1)	4e (36)
EtI (2.2)	4f (84)
PhCH ₂ Br (2.2)	4g (79)
Br(CH ₂) ₄ Br (1)	4h (67)
Br(CH ₂) ₅ Br (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 cm³) 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. NaHCO₃ (20 cm³) and extracted with dichloromethane (3 × 25 cm³). 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.

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 (R¹ ≠ R² ≠ H) by a second separate alkylation of the monoalkylated materials using the same method have so far failed.

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-H₂O, 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 alkanolic acids^{3a} and ketones⁷), and in a new route to imidazo[1,2-*a*]pyridines.

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

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