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CONDENSATION REACTIONS OF α-LITHIO-IMIDAZOLINES: PREPARATION AND CONJUGATE ADDITIONS OF 2-ALKENYL-2-IMIDAZOLINES.

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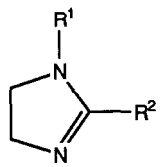
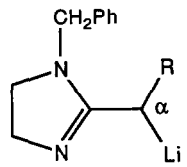
Summary: Whereas 1-benzyl-2-lithiomethyl-2-imidazoline undergoes reversible 1,2-addition to aldehydes and ketones, a derived phosphonate salt affords the condensation products, 2-(1-alkenyl)-2-imidazolines; the latter undergo conjugate addition with carbon nucleophiles.

Motivated by the wish to use the heterocycle 2-imidazoline (4,5-dihydroimidazole; 1) in the transfer of functionalised carbon atoms (as does Nature via the tetrahydrofolate coenzymes), and by the biological activity of many 2-imidazolines, we have reported the C-alkylation and C-acylation of 2-(α-lithioalkyl)-2-imidazolines (2);[1] these studies have led to a synthesis of carboxylic acids and of ketones. We wished to extend this work to produce



(1)



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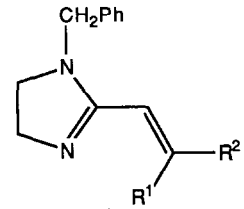
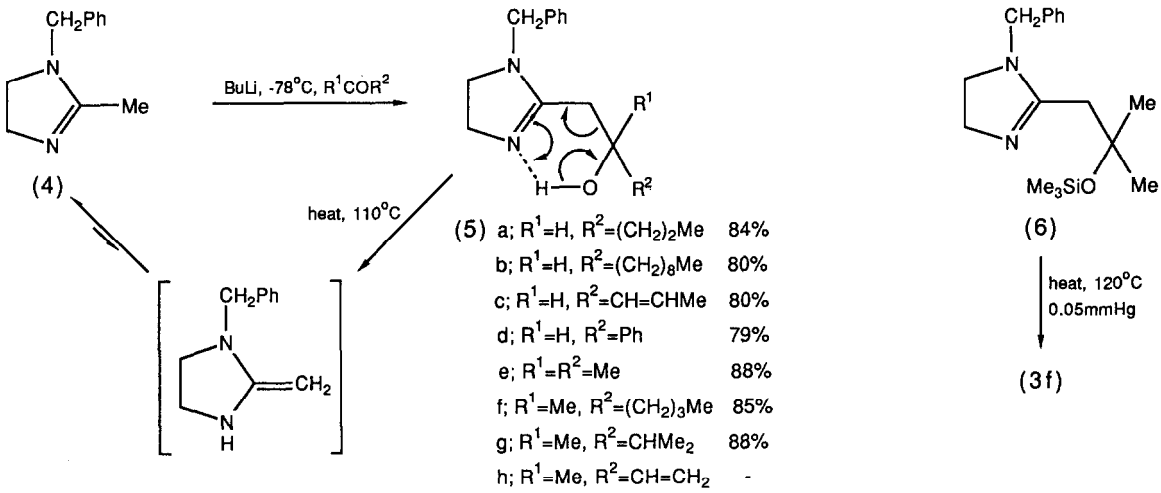


(3)

2-(1-alkenyl)-2-imidazolines (3) in order to examine their potential as acceptors in conjugate additions and as 1-azadienes in cycloaddition processes;[2] some 2-alkenyl-2-imidazolines have also been reported to have biological activity, e.g. anthelmintic[3] or hypoglycemic.[4] This Letter describes the (reversible) addition of (2; R=H) to aldehydes and ketones,[5] a successful protocol for the synthesis of 2-alkenylimidazolines (3) via a phosphonylation sequence, and preliminary studies of conjugate additions to (3).[6]

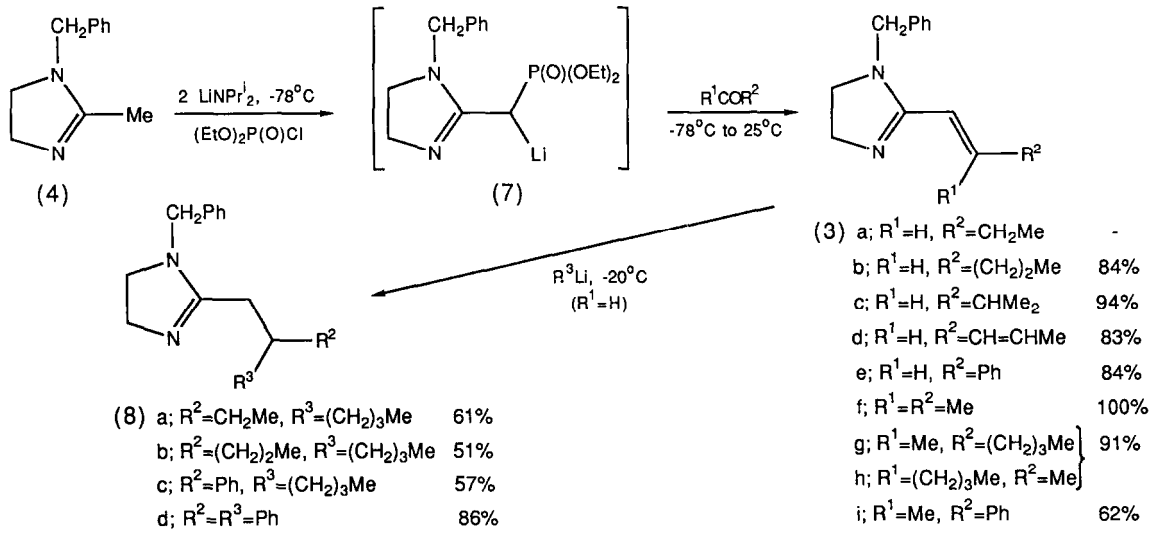
Our initial plan for the synthesis of compounds (3) involved addition of the anion (2; R=H) to aldehydes and ketones and dehydration of the



SCHEME 1

adducts formed. Indeed, lithiation of 1-benzyl-2-imidazoline (4) as usual[1] (BuLi, THF, -78°C) followed by addition of a range of aldehydes and ketones led in good yield to the 2-(2-hydroxyalkyl)imidazolines (5a-h) (Scheme 1).[7] Reaction with α,β-unsaturated aldehydes and ketones gave exclusively 1,2-addition (5c,h). On standing at room temperature, however, adducts (5) exhibit (p.m.r.) an increasing contamination with the 2-methylimidazoline (4). Attempted purification of (5) by distillation at reduced pressure, or heating of (5) in toluene (reflux, 2 h), led to good recoveries of (4), i.e. 'retro-aldol' reaction. The facile reaction in a non-polar medium prompts us to tentatively suggest the 'retro-ene' pathway of Scheme 1 for this fragmentation. Attempts to trap the adducts (5) were successful in only one case. Addition of Me_3SiCl directly to the reaction mixture at 25°C after reaction between the lithio-imidazoline (2; R=H) and acetone afforded (p.m.r.) the trimethylsilyl ether (6); thermolysis of the crude reaction mixture (120°C, 0.05 mm Hg) and distillation gave the 2-imidazoline (3f) (60%).[8] We could not extend this procedure to other examples. Various (mainly acidic) methods were investigated for elimination of water from (5) but again retro-aldol reaction was observed.[9]

Our attention therefore turned to promoting the elimination by the presence of a suitable heteroatom at the α-position. Thus the 2-methylimidazoline (4) was treated with $LiNPr^i_2$ (2 equiv., THF, -78°C) followed by diethylchlorophosphate (1 equiv.), and the phosphonate salt (7) so produced was quenched at -78°C with a range of aldehydes and ketones. After 16h at 25°C the 2-alkenyl-2-imidazolines (3a-i) were isolated in good yield (Scheme 2) from chromatography on alumina[10] and characterised as the oxalate salts.[11] Condensations with aldehydes afforded exclusively the E-alkenes (3a-e) (p.m.r.), whereas unsymmetrical ketones gave a mixture of geometric isomers.[12] 2-Hexanone, for example, produced (3g):(3h) (E:Z) 2:1; the crude product from acetophenone indicated an 8:1 E:Z ratio but acid-base extraction gave pure E-isomer (3i) directly.



(4) (7)

(3) a; R^1=H, R^2=CH_2Me -
b; R^1=H, R^2=$(CH_2)_2Me$ 84%
c; R^1=H, R^2=$CHMe_2$ 94%
d; R^1=H, R^2=CH=CHMe 83%
e; R^1=H, R^2=Ph 84%
f; R^1=R^2=Me 100%
g; R^1=Me, R^2=$(CH_2)_3Me$ } 91%
h; R^1=$(CH_2)_3Me$, R^2=Me }
i; R^1=Me, R^2=Ph 62%

(8) a; R^2=CH_2Me, R^3=$(CH_2)_3Me$ 61%
b; R^2=$(CH_2)_2Me$, R^3=$(CH_2)_3Me$ 51%
c; R^2=Ph, R^3=$(CH_2)_3Me$ 57%
d; R^2=R^3=Ph 86%

SCHEME 2

Having established a viable access to 2-alkenyl-2-imidazolines (3), we have performed some preliminary experiments to determine their potential as acceptors for conjugate addition of nucleophiles. Our previous work has shown that the 2-imidazoline ring is stable towards addition of organometallic reagents at C-2,[1] and Grignard reagents showed no reaction with the alkenylimidazolines (3). In contrast, treatment of the 2-(1-butenyl),2-(1-pentenyl), and 2-(2-phenylethenyl) compounds (3a), (3b), and (3e), respectively, with butyl- and phenyllithiums (THF; -20°C) afforded the corresponding 1,4-adducts (8a-d) in moderate yields (Scheme 2). Taken with our methods for cleavage of the imidazoline moiety,[1] such additions constitute a route to β-substituted carboxylic acids and ketones.

Reaction of (3e) with the softer nucleophile sodium diethyl malonate [$CH_2(CO_2Et)_2$, NaOEt (catalytic), EtOH, reflux] gave a crude product whose p.m.r. spectrum was consistent with the 1,4-adduct (9) (Scheme 3) and from which on chromatography over silica was isolated the cyclol (11) (52%), presumably formed via cyclisation of (9) to the hexahydroimidazo[1,2-a]pyridone (10) and hydration.[13]

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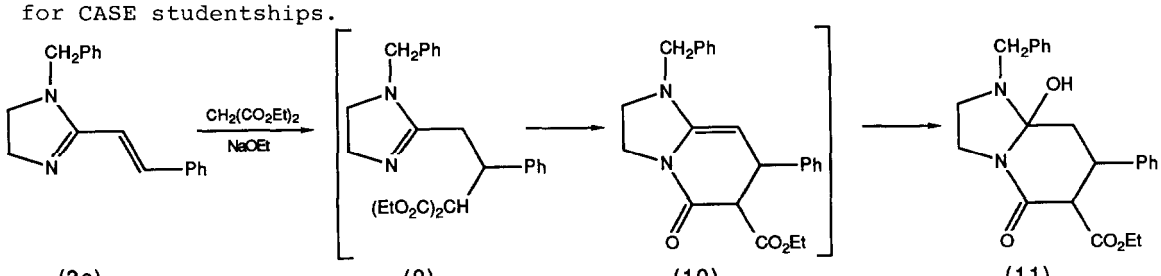

(3e) (9) (10) (11)

SCHEME 3

References and Notes:

1. M.W. Anderson, R.C.F. Jones, and J. Saunders, J.Chem.Soc., Perkin Trans.1, 1986, 205, 1995; M.W. Anderson, M.J. Begley, R.C.F. Jones, and J. Saunders, ibid., 1984, 2599.
2. Imidazoline derivatives have recently been reported as dienophiles in cycloadditions: U. Gruseck and M. Heuschmann, Tetrahedron Lett., 1987, 28, 2681; cf. also A. Pouilhés, C. Kouklovsky, N. Langlois, and Y. Langlois, ibid., p.6183.
3. J.W. McFarland, L.H. Conover, H.L. Howes, J.E. Lynch, D.R. Chisholm, W.C. Austin, R.L. Cornwell, J.C. Danilewicz, W. Courtney, and D.H. Morgan. J.Med.Chem., 1969, 12, 1066.
4. F. Ishikawa, Chem.Pharm.Bull., 1980, 28, 1394.
5. A limited number of adducts and condensation products between (mainly aromatic) aldehydes or ketones and 2-substituted-2-imidazolines have been reported: refs. 2, 3, and T. Shiba, K. Sawada, and Y. Hirotsu, Heterocycles, 1978, 10, 133.
6. For related studies with 2-oxazolines, see: A.I. Meyers, R.K. Smith, and C.E. Whitten, J.Org.Chem., 1979, 44, 2250; J. Clinet and G. Balavoine, Tetrahedron Lett., 1987, 28, 5509.
7. We thank Simon C. Hirst for the preparation of (5h). The yields given for (5a-g) are of material isolated directly from an aqueous work-up and giving satisfactory spectral data (IR, NMR); further purification led to some retro aldol reaction (vide supra). All other new compounds gave spectra in accord with the assigned structures (IR, NMR, MS) and satisfactory combustion analysis on accurate mass measurement. Purity was also assessed by t.l.c. examination.
8. Attempts to remove the LiCl present by aqueous extraction merely removed the labile trimethylsilyl group.
9. We acknowledge R.M. McMahon, P. Mellish, and J. Saunders (ICI Pharmaceuticals) for some additional experiments.
10. Substantial decomposition occurred on silica.
11. Oxalate salts (from ethanol-ether): (3b) m.p.113-114°C; (3c) m.p.122-124°C; (3d) m.p.141-143°C; (3e) m.p.130-132°C; (3f) m.p.80-82°C; (3g) m.p.108-109°C. All had combustion analysis consistent with a 1:1 imidazoline:oxalic acid stoichiometry. Imidazoline (3e) recovered from the oxalate salt was a yellow solid, m.p.80-82°C.
12. Selected p.m.r. data ($CDCl_3$): (3a) δ6.05 (1H, d, J 16 Hz, $\underline{CH}$=$CHCH_2$), 6.7-7.05 (1H, dt, J 16 and 7 Hz, CH=$\underline{CH}CH_2$); (3b) 2.0-2.3 (2H, m, CH=$CH\underline{CH_2}$), 6.05 (1H, d, J 18 Hz, $\underline{CH}$=$CHCH_2$), 6.6-7.0 (1H, dt, J 18 and 6 Hz, CH=$\underline{CH}CH_2$); (3c) 6.05 (1H, d, J 18 Hz, $\underline{CH}$=CHCH), 6.6-7.0 (1H, dd, J 18 and 6 Hz, CH=$\underline{CH}$CH); (3e) 6.65 and 7.7 (each 1H, d, J 17 Hz, $\underline{CH}$=$\underline{CH}$); (3f) 1.85 and 2.05 (each 3H, d, CH=$\underline{CMe}_2$), 5.75 (1H, s, $\underline{CH}$=$\underline{CMe}_2$); (3g,h) 1.85 [1H, d, CH=$\underline{CMe}CH_2$, (3h)], 2.05 [2H, d, CH=$\underline{CMe}CH_2$, (3g)], 2.15 [1H, t, CH=CMe$\underline{CH_2}$, (3g)], 2.5 [0.66 H, t, CH=CMe$\underline{CH_2}$, (3h)], 5.75 [1H, m, $\underline{CH}$=$CMeCH_2$, (3g/h)]; (3i) 2.45 (3H, s, CH=$\underline{CMe}$Ph), 6.3 (1H, s, $\underline{CH}$=CMePh).
13. Cf. R.C.F. Jones and M.J. Smallridge, accompanying Letter. Cyclol (11): $\nu_{max.}$ (film) 3350, 1740, 1680 cm^{-1}; δ1.1 (3H, t, Me), 1.6 (1H, br.s, OH), 2.8-3.05 (4H, m, $PhCH_2$ NCH_2 and $PhCHCH_2$), 3.65-3.95 (4H, m, $PhCH_2$ and 2 x CH), 3.95-4.25 (4H, m, OCH_2Me and CH_2NCO), and 7.15-7.55 (10H, m, 2 x Ph); m/z 376 (M^+-H_2O).

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