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IMIDAZOLINES IN SYNTHESIS, I: LITHIO IMIDAZOLINES - FORMATION AND C-ALKYLATION

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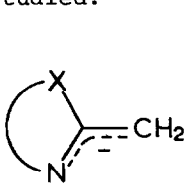
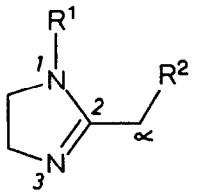
Summary - 2-Methyl-2-imidazolines have been lithiated and then C-alkylated; further metallation - alkylation of the products has been completed. Hydrolysis of the products to carboxylic acids completes a homologation, the imidazoline providing a two-carbon unit.

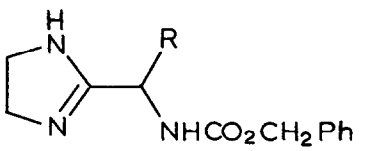
In recent years many reports have detailed the generation, reactivity, and synthetic application of anions (I) from heterocyclic systems such as 5,6-dihydro-4H-1,3-oxazines,[1] 2-oxazolines,[2] 2-thiazolines,[3] and benzothiazoles.[4] The 2-imidazoline system (II) has in contrast been much less well studied.[5]



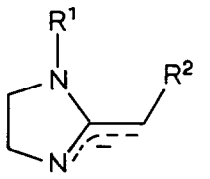
(I) X = O,S



II



III

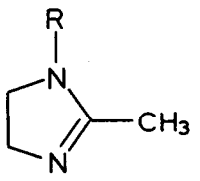


IV

The lability of α-hydrogens in (II) can be recognised in, for example, the epimerisation of imidazoline derivatives (III) of α-amino acids,[6] and the preparation of a limited number of adducts and condensation products between aldehydes and the α-positions of 2-substituted-2-imidazolines.[7] To date, however, no systematic investigation into the controlled formation and reactivity of imidazoline anions (IV) has been reported. We wish to disclose preliminary findings of such a study in our laboratories prompted by the synthetic potential of the system and by the biological activity shown by many imidazolines.

Initial studies used commercially available 2-methyl-2-imidazoline with the NH function masked as the t-butyldimethylsilyl (TBDMS) derivative (Va)

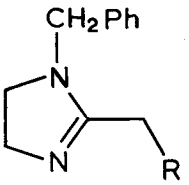
(the corresponding trimethylsilyl compound proved extremely moisture sensitive). Anion formation (Bu^nLi, various temperatures) and alkylation ($PhCH_2Br$) was successful, but yields of C-alkylation product (2-phenethyl-2-imidazoline after acid work-up) were non-reproducible and at best only moderate; similar results were obtained with other alkylating agents (MeI, $CH_2=CHCH_2Br$). Since the TBDMS group appeared unsatisfactory, subsequent work utilised 1-benzyl-2-methyl-2-imidazoline (Vb), easily prepared from N-benzyl-1,2-diamino-ethane and ethyl acetimidate hydrochloride. The lability of methyl protons in (Vb) was confirmed by n.m.r. spectral examination after treatment with D_2O-THF at 20°C; rapid deuterium incorporation with decrease in methyl signal was observed.



V

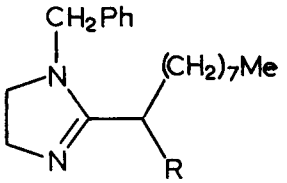
a; R = $SiMe_2Bu^t$

b; R = CH_2Ph



VI

R various



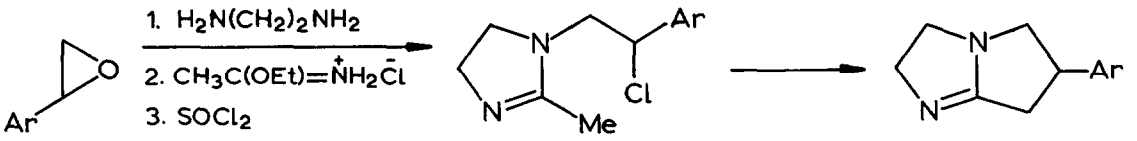
VII

R various

Satisfactory conditions for lithiation of (Vb) were treatment in THF with Bu^nLi (1.1 equiv.) in hexane at -78°C for 1 h. C-Alkylation of the anion was achieved with a wide variety of alkyl halides RX (see Table, entries 1-9) by addition of the halide (1.1 equiv.) at -78° and allowing the mixture to warm to 20°C over 1 h. When reaction was complete (a further 2 h for primary iodides, longer for bromides or secondary iodides) the alkylation products (VI) were isolated, after aqueous work-up and Kugelrohr distillation, in 78-89% yield.[8] When excess of MeI (3 equiv.) was used as alkylating agent, simple filtration of the reaction mixture after 18 h afforded 1-benzyl-2-ethyl-3-methyl-2-imidazolinium iodide, m.p. 83-85°C (88%).[8] C-Alkylation failed with cyclohexyl iodide.

The possibility of anion formation from a methylene rather than a methyl group, and the potential for two successive C-alkylations of 2-methyl compound (Vb), was confirmed by lithiation of 1-benzyl-2-nonyl-2-imidazoline [(VI), $R=(CH_2)_7Me$] by the same method (Bu^nLi, -78°C, 1 h) and subsequent alkylation with several alkyl halides RX (Table, entries 10-13) to give α,α-disubstituted imidazolines (VII).[8,9]

We have applied this new methodology to the synthesis of a pharmacologically interesting bicyclic imidazoline. Intramolecular C-alkylation (Bu^nLi or $LiNPr^i_2$) of the 1-(2-chloro-2-arylethyl)-imidazoline (VIII), prepared as shown, gave (IX), oxalate m.p. 199-200°C,[8] a centrally acting antihypertensive agent.[10]



VIII IX

(Ar=2,6-dichlorophenyl)

To demonstrate the synthetic potential of imidazolines as carboxylic acid precursors, hydrolytic cleavage of the 2-nonyl compound [(VI), R=$(CH_2)_7$Me] was examined. Mild basic attack (0.0375 M NaOH in ethanol[11]) gave an amide, believed to be $PhCH_2NH(CH_2)_2NHCO(CH_2)_8Me$, that afforded decanoic acid (66%) on acid treatment (6M HCl, reflux, 3 h). Acid hydrolysis of the imidazoline (65% H_2SO_4 aq., reflux) also afforded decanoic acid (65%); the 2-pentyl analogue [(VI), R=$(CH_2)_4Me$] likewise yielded hexanoic acid (71%). We are currently investigating alternative approaches to facilitate hydrolysis-cleavage.[12]

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TABLE : Alkylation of Lithio Imidazolines

	Alkyl Halide RX	VI:R=	VII;R=	Rn.time at 20°C	Yield (%)
1	CH_3I	CH_3		2 h	85
2	CH_3CH_2I	CH_3CH_2		"	89
3	$CH_3(CH_2)_3I$	$CH_3(CH_2)_3$		"	82
4	$CH_3(CH_2)_3Br$	"		5 h	79
5	$CH_3(CH_2)_7$ I	$CH_3(CH_2)_7$		4 h	88
6	$(CH_3)_2CHI$	$(CH_3)_2CH$		"	88
7	$(CH_3)_2C=CHCH_2Br$	$(CH_3)_2C=CHCH_2$		2 h	84
8	$PhCH_2Br$	$PhCH_2$		4 h	78
9		-		2 h	0
10	CH_3I		CH_3	"	69
11	$CH_3(CH_2)_3I$		$CH_3(CH_2)_3$	"	81
12	$(CH_3)_2CHI$		$(CH_3)_2CH$	"	80
13	$PhCH_2Br$		$PhCH_2$	"	56

References

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3. e.g. A.I. Meyers et al., J. Org. Chem., 1975, 40, 2021, 2025; T. Okutome, Y. Sakurai, M. Kurumi, H. Kawamura, S. Sato, and K. Yamaguchi, Chem. and Pharm. Bull (Japan), 1975, 23, 48.

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5. cf. J.V. Hay, D.E. Portlock, and J.F. Wolfe, J. Org. Chem., 1973, 38, 4379 for a report of the formation and reactivity of dilithio derivatives of the related 2-substituted benzimidazole system.

6. K. Yonetani, Y. Hirotsu, and T. Shiba, Bull. Chem. Soc. Japan, 1975, 48, 3302.

7. e.g. (a) 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. Medicin. Chem., 1969, 12, 1066; (b) T. Shiba, K. Sawada, and Y. Hirotsu, Heterocycles, 1978, 10, 133; (c) F. Ishikawa, Chem. Pharm. Bull. (Japan), 1980, 28, 1394.

8. All new compounds gave spectra (IR, NMR, MS) consistent with the assigned structure, and satisfactory accurate mass measurement or combustion analysis. Purity was assessed also by t.l.c. and g.l.c. examination.

9. Yields of (VII) were assessed by g.l.c. Reaction times are not optimised.

10. D.P. Clough, R. Hatton, S.J. Pettinger, G.M.R. Samuels, and A. Shaw, Brit. J. Pharmacol., 1978, 62, 385.

11. B.G. Harnsberger and J.L. Riebsomer, J. Heterocyclic Chem., 1964, 1, 188.

12. Treatment of the 2-nonyl imidazoline [(VI), R=$(CH_2)_7Me$] with 6M HCl at reflux gave low yields of decanoic acid (23%), whilst treatment with HCl (g) in methanol afforded only 9% of methyl decanoate. This reluctance to hydrolyse has been recorded elsewhere and attributed to resonance in the protonated imidazoline[7b]; N-sulphonation was suggested to facilitate the hydrolysis. Attempted transamidination (liq. NH_3) of [(VI), R=$(CH_2)_7Me$] has to date proved unsuccessful.

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