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NUCLEOPHILIC ATTACK ON 2-(4-OXOALKYL)-2-IMIDAZOLINES: A NOVEL ROUTE TO TETRAHYDROPYRIDINES AND PIPERIDINES

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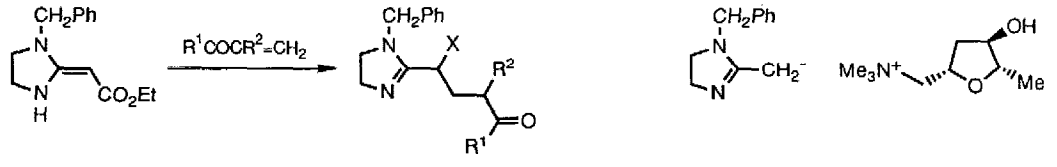
Summary: 2-(1-Ethoxycarbonyl-4-oxoalkyl)-2-imidazolines add organometallic carbon nucleophiles to produce new lactones, whereas hydrogenation affords 1,4,5,6-tetrahydropyridines and piperidines via a novel reductive cyclisation-cleavage pathway.

We have recently reported (Scheme 1) the synthesis of 2-(4-oxoalkyl)-2-imidazolines (2) and (3) by the conjugate (1,4) addition to α,β-unsaturated ketones of the enaminoester (1),[1] acting as an equivalent to the 2-imidazoline (4,5-dihydroimidazole) nucleophile (4).[2] Our motivation for exploring the conjugate additions had been to access potential acetylcholine agonists at muscarinic receptors (muscarine;5); with the amidine function (protonated at physiological pH) mimicing the quaternary nitrogen, we envisaged the imidazoline unit linked through C-2 to an oxygen heterocycle as a target framework.[1] The reaction of nucleophiles with the ketone function of adducts (2) with subsequent lactonisation looked suited to generate such a system. We report here the reaction of nucleophiles with the adducts (2). Carbon nucleophiles indeed form new lactones of potential biological interest, but with hydride nucleophiles and other reductive conditions the reaction takes a completely different course and provides a novel synthesis of tetrahydropyridines and piperidines.



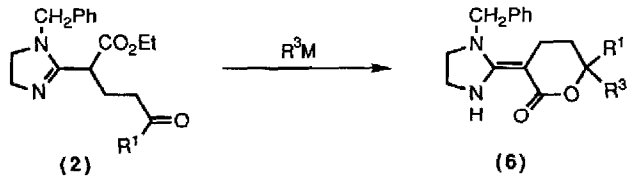
(1) (2) X= CO_2Et (3) X= H (4) (5)

H_3O^+

a; R^1= Me, R^2= H b; R^1= Et, R^2= H
c; R^1= Ph, R^2= H d; R^1= R^2= Me

Scheme 1

Treatment of the ethoxycarbonyl-substituted adducts (2a-c) in ether at 0°C with a range of Grignard reagents (methyl-, 1-butyl-, 2-propyl-, and phenyl-magnesium halides, 3 mol equiv.) led to a suspension, presumed to be of the corresponding magnesium alkoxides derived from nucleophilic addition to the ketone carbonyl group. Lactonisation was achieved by addition of THF (to partially solubilise the alkoxide) and heating at reflux for 20h to afford the range of new lactones (6a-i) (Table).[3] These lactones are formulated as the enaminolactone tautomers on the basis of spectroscopic evidence; they display the same chromophore as the enaminoester (1),[2d] and their i.r. and n.m.r. spectra provide evidence for the NH function and conjugated ester group [for example for (6a): $\lambda_{max.}$(EtOH) 289nm; $\nu_{max.}$($CHCl_3$) 3290 and 1630cm^{-1}; δ_H($CDCl_3$) 9.35 (1H, br s, NH); δ_C($CDCl_3$) 75.9 (NC=*C*CO) and 164.8 (CO); cf. (1): $\lambda_{max.}$(EtOH) 272nm]. The lactones (6) could also be generated by addition of alkyl-lithiums to the adducts (2) in ether-THF at -20°→20°C, but generally in lower yields than with

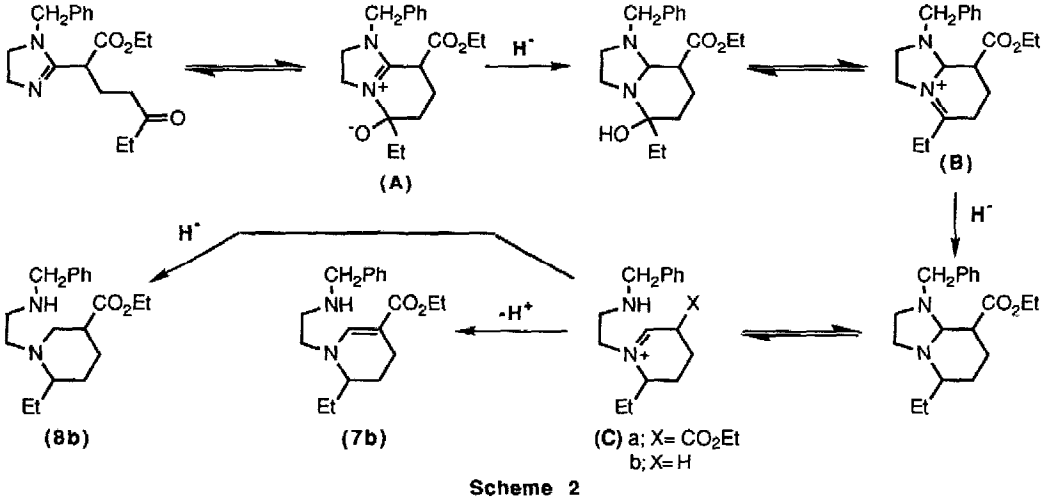


TABLE

Adduct	R^1	R^3	M	Lactone (6)	Yield (%)
(2a)	Me	Me	MgBr	(6a)	78
	Me	Me	Li	(6a)	22
	Me	$(CH_2)_3Me$	MgBr	(6b)	50
	Me	$CHMe_2$	MgCl	(6c)	34
	Me	Ph	MgBr	(6d)	94
	Me	Ph	Li	(6d)	44
(2b)	CH_2Me	Me	MgBr	(6e)	56
	CH_2Me	$CHMe_2$	MgCl	(6f)	46
	CH_2Me	Ph	MgBr	(6g)	69
(2c)	Ph	Me	MgBr	(6d)	61
	Ph	Me	Li	(6d)	50
	Ph	$CHMe_2$	MgCl	(6h)	71
	Ph	Ph	MgBr	(6i)	70

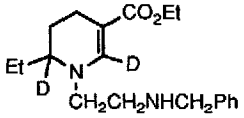
the corresponding Grignard reagents (Table). Presumably enolisation of the adducts by the more basic organolithiums is a competing process.Molecular mechanics studies[4] of the lactones (6) predict a relatively rigid structure with a separation of C-2 of the nitrogen heterocycle from the alkyl oxygen of the lactone of 3.67 Å, which compares well with a calculated separation (3.33 Å) of the quaternary nitrogen and the alkyl oxygen of acetyl-choline in a minimum energy conformation.[5] The lactones (6) are the subject of biological evaluation.

When we attempted to extend this work to hydride nucleophiles (to access mono-alkyl lactones) the reaction was found to take a very different course. Using adduct (2b), various trial experiments afforded no evidence of the lactones. Instead, from reductions with $NaBH_4$, we identified two products, the tetrahydropyridine (7b) and piperidine (8b), in variable yield (4% and 23%, respectively, at -20°C in EtOH). These unexpected structures were supported by spectral data including ^1H-^1H and ^1H-^{13}C COSY experiments.[6] A reduction with $NaBD_4$ (EtOH, -20°C) afforded the tetrahydropyridine (9) (39%) incorporating deuterium at C-2 and C-6. This led us to

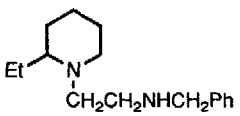


Scheme 2

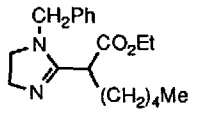
the mechanistic proposal of Scheme 2 in which the successive formation and trapping by hydride of three iminium ions (A, B, and Ca) leads to the piperidine (8b) and the alternative proton loss from the third iminium ion (Ca) affords the tetrahydropyridine (7b). Support for this Scheme was provided by the following. Reduction of the Michael adduct (3b) lacking the ethoxycarbonyl group (where proton loss before the third reduction is expected to occur less readily) afforded the piperidine (10) (22%) with no evidence of any tetrahydropyridine. No reduction was observed when the enaminoester (11) [formed by C-alkylation of (1); 1-iodo-pentane, EtOH reflux] was subjected to the same conditions, indicating that an initial interaction of N-3 of the imidazoline ring with the ketone oxygen is necessary.



(9)



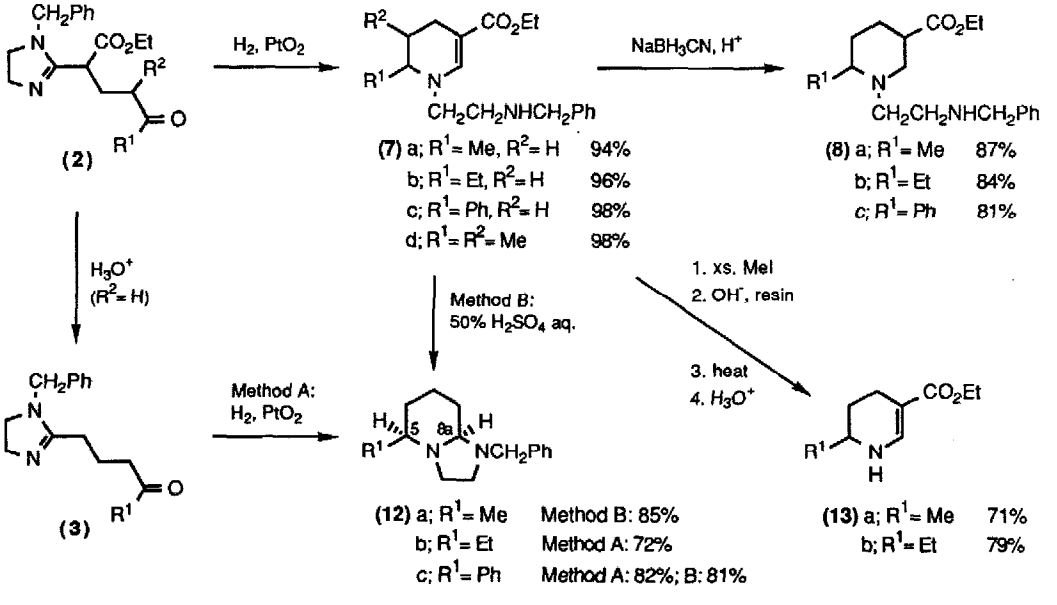
(10)



(11)

In an attempt to optimise this novel reductive cyclisation-cleavage, various reducing agents were surveyed. Other hydride reagents gave similar results to $NaBH_4$. Reaction of (2a) with diborane (THF, 0°C, 2h) afforded the tetrahydropyridine (7a) (97%);[7] addition of $BF_3.Et_2O$ to (2a) before the diborane led to the piperidine (8a) (82%).[8] Eventually hydrogenation of the adducts (2) over PtO_2 (1 atm H_2, EtOH, 20°C) was found to produce the tetrahydropyridines (7a-d) in excellent yield (Scheme 3).[9] The piperidines (8a-c) were now obtained in good yield from (7) by hydride reduction under acidic conditions ($NaBH_3CN$, MeOH-HCl aq., pH4.5), thus providing predictable and efficient access to both of the original reduction product types.

Hydrogenation under the same conditions of the adducts (3) lacking the ethoxycarbonyl unit was observed to afford the bicyclic octahydroimidazo[1,2-*a*]pyridines (12b,c).[6] The general pathway is thus being followed once again with termination of the sequence at the bicycles (12) before formation of the third iminium ion,[10] suggesting that the final equilibrium is unfavourable and is only observed where (C) can be trapped, e.g. by



Scheme 3

hydride reagents or by proton loss. This conclusion was reinforced by the alternative preparation of bicycles (12a,c) when the tetrahydropyridines (7a,c) were treated with 50% H_2SO_4 aq. (80°C, 1h) to remove the ethoxycarbonyl group.[11] Presumably iminium ions (Cb) are intermediates here, trapped intramolecularly by the pendant amino nitrogen atom. The octahydroimidazopyridines (12) were formed from both routes exclusively as the cis-diastereoisomers illustrated, as shown by a strong n.O.e. between the hydrogen atoms at C-5 and C-8a indicating a 1,3-diaxial relationship across the piperidine ring.

The pendant N-[2-(benzylamino)ethyl] group can be removed from the tetrahydropyridines (7) by a Hofmann elimination sequence. Exhaustive methylation (MeI, 5 mol equiv., NaH, THF reflux) at the more basic nitrogen atom, anion exchange (Amberlite IRA-400, OH^- form) and distillation-pyrolysis of the quaternary ammonium hydroxide (170°C, 0.4 mmHg) was followed by an acidic work-up (2M HCl aq.) to hydrolyse the (presumed) enamine formed, with isolation of the NH-tetrahydropyridines (13a,b).[6]

The tetrahydropyridines prepared herein are of potential biological interest. We are currently exploring the scope of this novel piperidine synthesis and in particular the application of tetrahydropyridines (7) and (13), and bicycles (12), and their derivatives in routes to 2,6-disubstituted piperidine alkaloids. We thank Drs. E.W. Collington and P. Hallett for helpful discussions, and Glaxo Group Research and SERC for a CASE studentship (to S.C.H.).

References and Notes

1. R.C.F. Jones and S.C. Hirst, preceding *Letter*.
2. (a) R.C.F. Jones, M.W. Anderson, and M.J. Smallridge, *Tetrahedron Lett.*, 1988, **29**, 5001; (b) R.C.F. Jones and M.J. Smallridge, *Tetrahedron Lett.*, 1988, **29**, 5005; (c) M.W. Anderson, R.C.F. Jones, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1986, 205, 1995; (d) M.W. Anderson, M.J. Begley, R.C.F. Jones, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2599; (e) R.C.F. Jones, J. Schofield, and M.J. Smallridge, unpublished results.
3. All new compounds gave spectral data (i.r., u.v., n.m.r., m.s.) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
4. Performed using the COSMIC force field; J.G. Vinter, A. Davis, and M.R. Saunders, *J. Comput.-Aided Mol. Design*, 1987, **1**, 31.
5. L.B. Kier, *Mol. Pharm.*, 1967, **3**, 487.
6. Selected spectroscopic data: (**7b**): $\nu_{max.}$(film) 3300, 1670, and 1610cm^{-1}; $\delta_H(CDCl_3)$ 3.09 (1H, m, CH_2CHN) and 7.39 (1H, s, NCH=C); $\delta_C(CDCl_3)$ 56.1 (CH_2CHN), 93.9 (CCO_2Et), 144.6 (NCH=C), and 168.5 (C=O); (**8b**): $\nu_{max.}$(film) 3300 and 1730cm^{-1}; $\delta_H(CDCl_3)$ 2.41 (1H, dt, *J* 13.0 and 4.3 Hz, CH_2CHN), 2.51 (1H, m, $CHCO_2Et$), 2.57 and 2.80 (each 1H, 2xm, $NCH_aH_bCHCO_2Et$); $\delta_C(CDCl_3)$ 40.3 ($CHCO_2Et$), 48.9 (CH_2CHCO_2Et), 59.4 (CH_2CHN), and 174.2 (CO); (**12c**): $\delta_H(CDCl_3)$ 2.65 (1H, dd, *J* 2.3 and 9.4 Hz, NCHN) and 3.12 (1H, dd, *J* 3 and 10.8 Hz, CH_2CHN); $\delta_C(CDCl_3)$ 68.3 (CH_2CHN) and 84.8 (NCHN); (**13b**): $\nu_{max.}(CHCl_3)$ 3440, 1675, and 1630cm^{-1}; $\delta_H(CDCl_3)$ 3.80 (1H, m, NH), 4.45 (1H, m, CH_2CHNH), and 7.50 (1H, d, *J* 5 Hz, NHCH=C); $\delta_C(CDCl_3)$ 52.1 (CH_2CHNH), 95.6 (CCO_2Et), 142.5 (NCH=C), and 168.8 (CO). A mixture of diastereoisomers was observed for (7d), estimated at 3:2 from the p.m.r. spectrum; likewise (8a-c) were isolated as 2:1 mixtures of diastereoisomers from cyanoborohydride reduction of (7a-c), although (8b) from the borohydride reduction of (2b) was isolated as a single diastereoisomer.
7. A similar result was observed with the borane-ethanolamine complex, giving (7a) in 79% yield.
8. The scope of these borane reductions has not been fully explored. Adduct (2c) was not reduced under the same conditions.
9. This is consistent with the hydrogenation of 3-acylpyridinium compounds, which stops at the 1,4,5,6-tetrahydropyridines unless forcing conditions are employed; R.L. Augustine, 'Catalytic Hydrogenation', Edward Arnold, London, 1965.
10. Although the mechanism of Scheme 2 may not apply exactly under the hydrogenation conditions, it must form a basis for the pathway and it provided the motivation for our search of various reducing conditions.
11. Treatment of (7) with MeOH-HCl aq., as for the conversion of (2) into (3), (ref. 1) gave incomplete reaction.

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