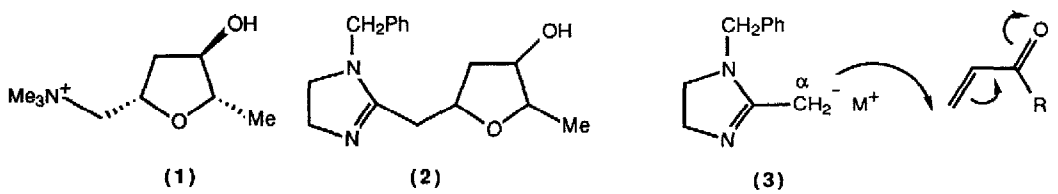
Tetrahedron Letters,Vol.30,No.39,pp 5361-5364,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CONJUGATE ADDITION OF IMIDAZOLINES: A PROTOCOL FOR 1,4-ADDITION TO ENONES AND OTHER ACCEPTORS

Raymond C.F. Jones * and Simon C. Hirst
(Chemistry Department, Nottingham University, Nottingham NG7 2RD, U.K.)

Summary: The enaminoester 1-benzyl-2-ethoxycarbonylmethyleneimidazolidine reacts with α,β-enones and other Michael acceptors to give 1,4-adducts; removal of the ethoxycarbonyl group completes overall conjugate addition of the imidazoline α-anion (which itself adds 1,2 to enones), and hydrolysis affords carboxylic acids.

In endeavouring to merge the known biological properties of many 2-imidazolines (4,5-dihydroimidazoles)[1] into a search for potential cholinergic agonists selective for muscarinic receptors (muscarine; 1), we generated a range of target structures, of which (2) is representative, and identified a key methodology for their construction as the conjugate (1,4) addition of the 2-imidazoline α-anion (3) onto Michael acceptors such as α,β-enones (Scheme 1). Defining the reactivity of 2-(α-lithiomethyl)-2-imidazolines (3; M= Li) has engaged us regularly during a programme to develop the imidazoline moiety as a vehicle for carbon-transfer processes related to those mediated by the tetrahydrofolate coenzymes.[2] Indeed we have previously reported that (reversible) addition of lithio-derivative (3; M= Li) to but-3-en-2-one occurs instead in the alternative 1,2-mode,[2a] in common with many anions of this type.[3]



(1) (2) (3)

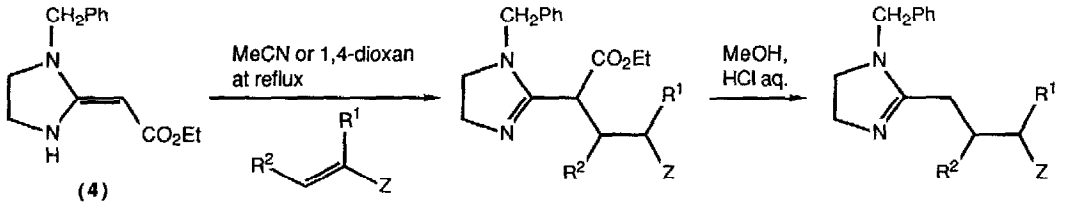
Scheme 1

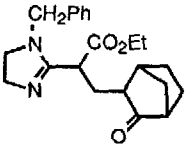
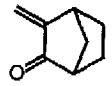
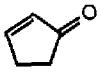
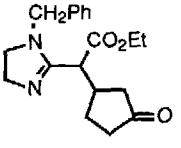
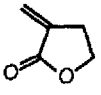
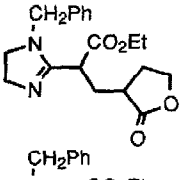
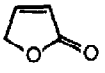
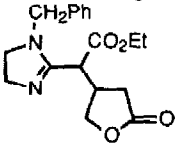
We report herein a new protocol for the successful completion of the conjugate addition to α,β-enones and other acceptors; subsequent cleavage of the heterocycle accomplishes a two-carbon transfer in a Michael sense. We further show that α,β-enals proceed beyond conjugate addition to afford 1,4-dihydropyridines of potential biological interest in an overall annulation.

An accepted strategy for directing 1,4-addition is to create a 'softer'[4] nucleophile. Attempted transmetallation of the lithio-imidazoline (3; M= Li) to form homo- or hetero-cuprates of various stoichiometries was however *uniformly unsuccessful,[3a] producing at best 3% of the 1,4-adduct with but-3-en-2-one. We therefore* determined to investigate as an alternative a delocalised nucleophile, the enaminoester (4).[2b,d] Deprotonation of enaminoester (4) was found to be unnecessary, as the enamine character conferred sufficient nucleophilicity, and treatment of (4) with but-3-en-2-one (5a) in MeCN (reflux, 4h) indeed afforded the 1,4-adduct (6a) (Scheme 2) in good yield (96%).[5] A range of other Michael acceptors (5b-l) was found to undergo smooth 1,4-addition to afford the adducts (6b-l), respectively, either in MeCN at reflux (conditions A) or in 1,4-dioxan at reflux

(conditions B) as indicated (Scheme 2).[5,6] Amongst the ketones, conditions A were adequate for those having unsubstituted vinyl groups (5a-c); 1-phenylpropen-1-one (5c) was prepared *in situ* from 3-chloro-1-phenylpropan-1-one and triethylamine.[7] Substitution α in the vinyl group (5d and e) retarded the addition whilst β-substitution hindered the reaction still further such that only in the case of cyclopentanone (5f) did we observe addition, and then only under conditions B.[8] Other acceptor types found to give 1,4-adducts included the unsaturated lactones (5g and h),[9] propenonitrile (5i), the vinyl sulphoxide (5j) and sulphone (5k) (the sulphone exhibiting higher reactivity than the sulphoxide), and vinyltriphenylphosphonium bromide (5l). In this latter case, no trapping of the intermediate ylid could be achieved, presumably because of rapid proton-transfer from the iminoester function.

In all cases the adducts (6) were observed to exist in solution predominantly as the illustrated imine

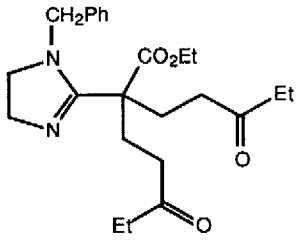


(5)	R^1	R^2	Z	Condns.	(6)		(8)
a	H	H	CO.Me	A	96%		52%
b	H	H	CO.Et	A	85%		92%
c	H	H	CO.Ph	A	82%		70%
d	Me	H	CO.Me	A	56%		
e				A	42%		
f				B	69%		
g				A	94%		89%
h				B	20%		
i	H	H	CN	A	79%		88%
j	H	H	SOPh	B	32%		
k	H	H	SO_2Ph	A	98%		94%
l	H	H	P^+Ph_3	A	84%		

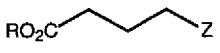
[Conditions A: MeCN, reflux
conditions B: 1,4-dioxan, reflux]

Scheme 2

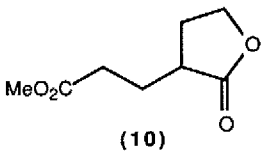
(imidazoline) tautomer rather than in the enamine form, as indicated in the u.v. spectrum by the absence of the enaminoester chromophore [enaminoester (4) has $\lambda_{max.}$ (EtOH) 272nm (ε $3.2x10^4$)], and by appropriate differences in the i.r. and p.m.r. spectra [(4): $\nu_{max.}$($CHCl_3$) 3380 br, 1640, and 1580cm^{-1}; δ_H($CDCl_3$) 7.7 (1H, br s, NH) and 4.26 (1H, s, vinyl CH); for example (6b): $\nu_{max.}$($CHCl_3$) 1740, 1605, and 1540cm^{-1}; δ_H($CDCl_3$) 3.52 (1H, t, *J* 6.5 Hz, $CHCO_2Et$)]. On the other hand in some instances, and particularly with the vinyl ketones if the stoichiometry (generally 1-1.2 mol equiv. of ketone) or conditions were varied, traces of double addition were observed, indicating that equilibrium of imidazolines (6) with the corresponding nucleophilic enamino-tautomer is at least accessible; for example (7) was isolated (10%) along with (6b) from the addition of (4) to pent-1-en-3-one (5b) (1.2 mol equiv.).



(7)



(9) a; R= H, Z= CO_2Me
b; R= H, Z= CO.Ph
c; R= Me, Z= SO_2Ph

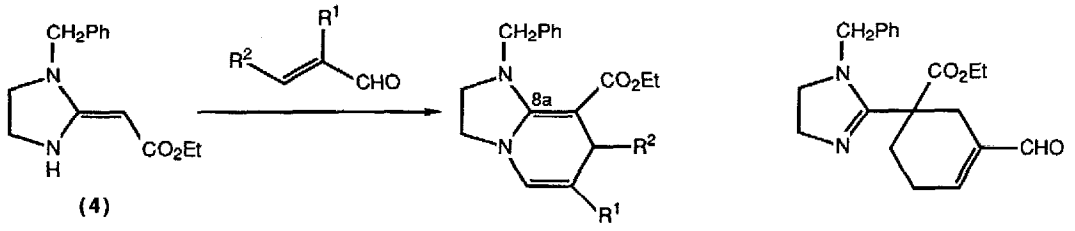


(10)

Removal of the ethoxycarbonyl activating group from the 1,4-adducts (6) was accomplished by treatment with MeOH containing 3% HCl by addition of 2M hydrochloric acid (reflux, 2-5 days), to afford the imidazolines (8a-c, g, i, and k) (Scheme 2) [for example (8b): $\nu_{max.}$($CHBr_3$) 1705 and 1595cm^{-1}; δ_H($CDCl_3$) 2.45 (6H, m, α-CH_2 and CH_2COCH_2)] in good yield, thus achieving in two steps our original objective of directing 1,4-addition of the synthon (3) to Michael acceptors. Under these conditions the lactone and nitrile groups (in 8g and 8i, respectively) remained intact. Cleavage of the heterocycle with concomitant decarboxylation, to demonstrate the imidazoline as a two-carbon transfer reagent, was completed under more vigorous hydrolysis conditions (55% H_2SO_4, reflux, 4-6h); thus reaction of adducts (6a), (6c), (6k), and (6g) afforded the acids (9a) (reaction at 20°C, 16h in this case; 83%) and (9b), m.p. 119-120°C (60%), and after addition of methanol to the acidic mixture from the hydrolysis (for ease of isolation), the esters (9c) (73%) and (10) (87%), respectively.

The reaction of enaminoester (4) with α,β-enals under comparable conditions did not afford simple 1,4-adducts. Instead further interaction between N-1 of the heterocycle and the aldehyde group of the (presumed) primary adducts to generate an enamine led to overall annulation (Scheme 3) to afford the fused 1,4-dihydropyridines (1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridines) (11a-d) [for example (11a): $\nu_{max.}$($CHCl_3$) 1665 and 1640cm^{-1}; δ_H($CDCl_3$) 1.00 (3H, d, *J* 8 Hz, *Me*CH), 3.75 (3H, m, NCH_2CH_2N and C*H*Me), 5.15 (1H, d, *J* 8 Hz, NC*H*=CH), and 6.00 (1H, t, *J* 8 Hz, NCH=C*H*)]; this conjugate addition-cyclocondensation sequence is supported by the lack of evidence for enamine formation between (4) and saturated aldehydes. The isolated yields of (11) were only moderate after chromatography; presumably water addition at C-8a to give cyclols is intervening[2b] [the increased yield of (11a) was secured by distillation rather than chromatography, which was not possible with (11b-d)]. In the case of enals, 1,4-addition was not prevented by β-substitution of the conjugated alkene. Indeed using propenal, the one example of a β-unsubstituted α,β-enal that we studied ,

the only product was not a dihydropyridine (11) but the cyclohexene (12) [$\nu_{max.}(CHCl_3)$ 1730, 1680, and 1600cm^{-1}; $\delta_H(CDCl_3)$ 6.81 (1H, dd, *J* 5.7 and 3.5 Hz, CH=C) and 9.48 (1H, s, CH=O); 59% based on (4), with 1.2 mol equiv. propenal, i.e. quantitative based on aldehyde] resulting from 1,4-addition of (4) to two molecules of aldehyde followed by intramolecular aldol condensation.



(11) a; R^1 = H, R^2 = Me 62%
b; R^1 = R^2 = Me 32%
c; R^1 = Me, R^2 = H 32%
d; R^1 = H, R^2 = Ph 27%

Scheme 3

Further reactions of the adducts (6) to form new lactones of potential biological interest and a novel synthesis of tetrahydropyridines and piperidines will be reported separately.[10] 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

1. See for example, R.J. Grout in 'The Chemistry of Amidines and Imidates', ed. S. Patai, Wiley, London, 1975, p. 255; C.B. Chapleo, *Chem. in Brit.*, 1986, 313.
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. (a) B.H. Lipshutz and R.W. Hungate, *J. Org. Chem.*, 1981, **46**, 1410; (b) A.I. Meyers, J.L. Durandetta, and R. Munavu, *J. Org. Chem.*, 1975, **40**, 2025; (c) A.I. Meyers, D.L. Temple, R.L. Nolen, and E.H. Mihelich, *J. Org. Chem.*, 1974, **39**, 2778; (d) J.V. Hay, D.E. Portlock, and J.F. Wolfe, *J. Org. Chem.*, 1973, **38**, 4379; (e) A.I. Meyers, A. Mabeya, H.W. Adickes, I.P. Politzer, G.R. Malone, A.C. Kovelevsky, R.L. Nolen, and R.C. Portnoy, *J. Org. Chem.*, 1973, **38**, 36.
4. T.-L. Ho, *Chem. Rev.*, 1975, **75**, 1.
5. 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.
6. Reaction times for the 1,4-additions varied from 4-72h; conditions B generally involved the longer reaction times. The imidazolines (6) and (8) were observed to undergo a slow retro-Michael reaction which could be inhibited by the formation of salts, for example with di-*p*-toluoyltartaric acid.
7. P.J. Thomas and C.J.M. Stirling, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1135.
8. Amongst the β-substituted α,β-enones that failed to undergo addition were hex-3-en-2-one, 1,5-diphenylpenta-1,4-dien-3-one, and 2-cyclohexenone. These reactions were not influenced by the addition of mild base (triethylamine), Lewis-acid (boron trifluoride etherate), or copper(II) acetoacetonate (P. Kocovsky and D. Dvorak, *Tetrahedron Lett.*, 1986, **27**, 5015).
9. With simple acyclic α,β-unsaturated esters the reaction is somewhat more complex, see ref. 2b.
10. R.C.F. Jones and S.C. Hirst, *Tetrahedron Lett.*, following Letter.

(Received in UK 19 July 1989)