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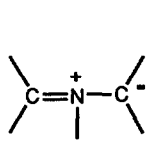
ANNULATION OF IMIDAZOLINES: A 1,3-DIPOLAR CYCLOADDITION ROUTE TO PYRROLOIMIDAZOLES, PYRROLIDINES AND PYRROLES

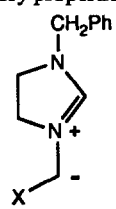
Raymond C.F. Jones,*[a] John R. Nichols,[a] and Michael T. Cox[b]
[a](Chemistry Department, Nottingham University, Nottingham NG7 2RD, U.K.)
[b](ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.)

Summary: Azomethine ylides, prepared from imidazolinium salts, undergo 1,3-dipolar cycloaddition with a variety of dipolarophiles to produce hexahydropyrrolo[1,2-*a*]imidazoles, which are reduced to pyrrolidines; with 2-chloroacrylonitrile as dipolarophile, pyrroles can be prepared from the cycloadducts by elimination.

The use of azomethine ylides (1) as 1,3-dipoles in cycloaddition reactions has received much attention recently as a route to new five-membered nitrogen-containing rings.[1] To date, however, there have been only limited reports of the use of amidines as a source of azomethine ylides.[2] As an extension to our studies on the annulation of imidazolines (4,5-dihydroimidazoles),[3] we now report the preparation and stereoselective cycloaddition reactions of the imidazolinium azomethine ylides (2) to produce novel hexahydropyrrolo[1,2-*a*]-imidazoles (3), and, by subsequent reduction or elimination, pyrrolidines and pyrroles. The fused imidazoles (3) are of interest (i) as analogues of naturally occurring pyrrolizidines, e.g. retronecine (4), the heterocyclic sub-unit of many of the toxic pyrrolizidine alkaloids,[4] and (ii) because pyrrolo[1,2-*a*]imidazoles have been reported to have anti-inflammatory properties.[5]



(1)



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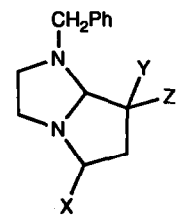

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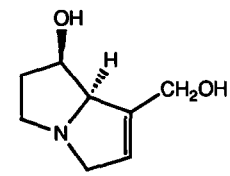
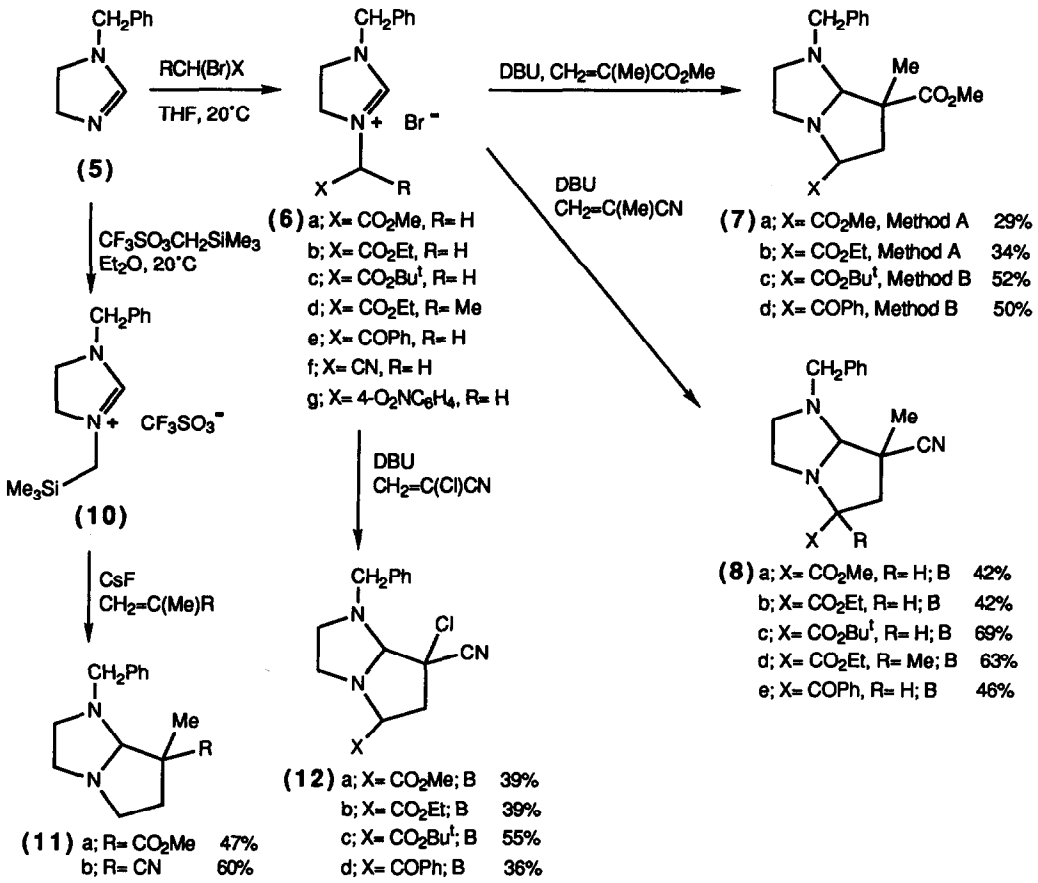


(4)

We first investigated stabilised azomethine ylides, that is those carrying an electron-withdrawing group attached to the formally negatively charged end of the dipole. The substrate was 1-benzyl-2-imidazoline (5),[6] which was first quaternised by reaction (THF, 20°C) with the α-haloesters methyl, ethyl, and t-butyl bromoacetate, and ethyl 2-bromopropionate, as well as with 2-bromoacetophenone, bromoacetonitrile, and 4-nitrobenzyl bromide to produce the salts (6a-g) (Scheme 1); the salts were isolated as hygroscopic solids or semi-solids in high yield by simple filtration or evaporation, and used directly. Attempts to use diethyl bromomalonate led merely to the hydrobromide salt of (5).

After investigating a range of bases and solvents for the generation of ylides from the ester salts (6a-d), two protocols were evolved for ylide formation and cycloaddition: (A) dropwise addition of diazabicyclo-[5.4.0]undec-7-ene (DBU) to a slurry of freshly prepared quaternary salt (6) in excess dipolarophile; and (B) very slow (over ≤ 4 h) addition of DBU to a solution of quaternary salt (6) and dipolarophile in THF at reflux. By these methods and using methyl methacrylate as dipolarophile, the pyrroloimidazole cycloadducts (7a-c)[7]



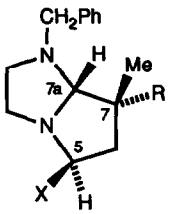
Scheme 1

were prepared regiospecifically (Scheme 1); use of methacrylonitrile as dipolarophile afforded the bicyclic products (8a-d)[7] as shown. Similarly, the salt (6e) led to bicycles (7d) and (8e)[7] using methyl methacrylate and methacrylonitrile, respectively. Method B was generally found to be more efficient; no cycloadducts could be isolated from reactions with salts (6f) and (6g). α-Methylstyrene was examined as a dipolarophile but failed to produce any cycloadducts, indicating that these azomethine ylides require electron-deficient dipolarophiles as cycloaddition partners.[8] The observed regiochemistry is as expected.[1b,d,9]

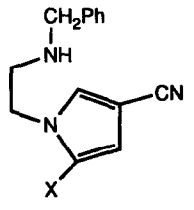
When the pyrroloimidazoles (7) and (8) were analysed by ^{1}H n.m.r. spectroscopy directly after chromatography over silica with an EtOAc: hexane eluent, they were seen to consist of a single diastereoisomer. On storage, or if the chromatography was performed with a basic eluent (CH_2Cl_2: EtOH: NH_3 aq. or EtOAc: Et_3N), then varying amounts of a second stereoisomer were encountered. The new isomer has been assigned as an epimer at C-7a of the primary cycloadduct (see also below). The relative stereochemistry of the primary products is proposed as (9) based on n.O.e. measurements in the ^{1}H n.m.r. spectra.[10] For example, in the diester (7a≡9a) irradiation of the C-7(Me) signal at δ 1.40 led to an enhancement of 2.5% of the bridgehead proton signal C-7a(H) with no change in the methine signal C-5(H); similarly for (8c≡9b), irradiation of C-7(Me) at δ 1.375 gave an enhancement of 2.1% at C-7a(H) δ 3.875, whilst irradiation of the double doublet

for C-5(H) at δ 3.675 gave no change in either the C-7a(H) or C-7(Me) signals. Other signals were consistent with this assignment, and the same behaviour was seen for ketone adducts (7d≡9c) and (8e≡9d).

The above cycloadditions could be extended to unstabilised imidazolinium azomethine ylides prepared by the protodesilylation strategy of Vedejs.[11] Thus the imidazoline (5) was converted to the salt (10) (Scheme 1) ($CF_3SO_3CH_2SiMe_3$, Et_2O, 20°C) which was added directly in diglyme to a slurry of excess CsF and a dipolarophile in diglyme. With methyl methacrylate and methacrylonitrile the pyrroloimidazoles (11a) and (11b)[7] were prepared (Scheme 1) as 1:1 and 2:1 mixtures of diastereoisomers, respectively (using basic eluents for their chromatography).



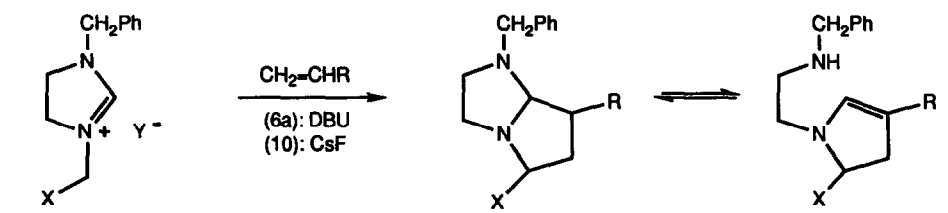
(9) a; X= R= CO_2Me
b; X= CO_2Bu^t, R= CN
c; X= COPh, R= CO_2Me
d; X= COPh, R= CN



(13) a; X= CO_2Et 73%
b; X= CO_2Bu^t 59%
c; X= COPh 50%

Attempts to utilise alkynes as cycloaddition partners for the azomethine ylides were unsuccessful, with alkyne polymerisation intervening under the basic reaction conditions. On the other hand, using 2-chloroacrylonitrile as an alternative dipolarophile at the same oxidation level, pyrroloimidazoles (12a-d) could be prepared by method B (Scheme 1); in these cases the adducts were formed as 1:1 mixtures of diastereoisomers, epimeric at C-7 (see below). Treatment of (12) with base (DBU, DMF, 100°C) resulted in a double elimination, presumably *via* initial loss of HCl to form the elusive alkyne cycloadducts, to afford the novel N-substituted pyrroles (13a-c).[7,12]

All of the dipolarophiles used to this point are substituted α- to the activating group. When cycloaddition partners lacking an α-substituent are employed, a ring-opening elimination is observed in equilibrium with the bicyclic adducts after chromatography. Thus salt (6b) with methyl acrylate and DBU gave a mixture (58%) of (14a) and the dihydropyrrole (15a) (Scheme 2); this mixture, for example, showed bands in the i.r. spectrum



(6) b; X= CO_2Et, Y= Br
(10) X= Me_3Si, Y= CF_3SO_3

(14) a; X= CO_2Et, R= CO_2Me
b; X= H, R= CO_2Me
c; X= H, R= COMe

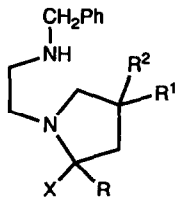
(15)

Scheme 2

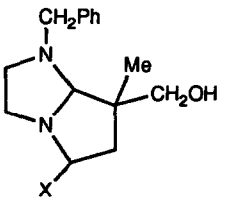
at 1730 (C=O, unconjugated ester), 1680 (C=O, conjugated ester), and 1600 cm^{-1} (C=C), and had *m/z* 322 (M^+). Likewise the salt (10) with methyl acrylate (CsF, diglyme) gave a mixture (43%) of (14b) and (15b) [$\nu_{max.}$ 1735, 1675, and 1599 cm^{-1}; *m/z* 260 (M^+)] and with but-3-en-2-one a mixture (73%) of (14c) and (15c) ($\nu_{max.}$ 1710, 1670, and 1570 cm^{-1}). This elimination is related to observations we have reported in the

six-membered series,[3a,13] and to that observed with the 2-chloroacrylonitrile adducts (see above).

It is possible to envisage the above equilibrium being established under basic conditions (self-catalysed, or during chromatography eluting with EtOAc: Et_3N or $CHCl_3$: Pr^iNH_2) or under acidic conditions *via* a protonation at N-1. This latter suggested a further modification of the cycloadducts (7), (8), (11), (12), and (14/15). Thus reduction under acidic conditions ($NaBH_3CN$, H^+) converted the appropriate pyrroloimidazoles into the substituted pyrrolidines (16a-e)[7] in high yields as single stereoisomers. These stereochemical results are consistent with the second stereoisomer that appears in the bicyclic materials (7) and (8) on standing being the C-7a epimer. Reduction of (12c) afforded (16f),[7] with an unchanged 1:1 diastereoisomer ratio, confirming that the isomers of (12) are epimeric at C-7 rather than C-7a (see above).



(16) a; X= CO_2Et, R= H, R^1= CO_2Me, R^2= Me 68%
b; X= CO_2Et, R= H, R^1= CN, R^2= Me 99%
c; X= CO_2Bu^t, R= H, R^1= CN, R^2= Me 86%
d; X= CO_2Et, R= Me, R^1= CN, R^2= Me 71%
e; X= H, R= H, R^1= CO_2Me, R^2= Me 82%
f; X= CO_2Bu^t, R= H, R^1= CN, R^2= Cl 86%
g; X= R^1= CH_2OH, R= H, R^2= Me



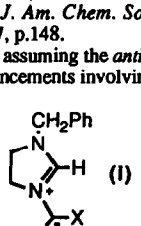
(17) a; X= CH_2OH 87%
b; X= H 98%

Reduction need not necessarily lead to ring opening. Treatment of (7c) with $LiAlH_4$ in Et_2O gave the bicyclic diol (17a) and similar treatment of (11a) gave (17b)[7] (still as a 1:1 diastereoisomer mixture). Hydrogenation of (17a) (1 atm., Pd/C) led to the pyrrolidine diol (16g) (70%).

We have thus defined conditions for the preparation of azomethine ylides from 2-imidazolines, for their use in annulation to pyrroloimidazoles, and for further conversions to pyrrolidines and pyrroles. We thank ICI Pharmaceuticals and SERC for a CASE studentship (to J.R.N.).

References

1. For example: (a) A.I.D. Alanine, C.W.G. Fishwick, and C. Szantay, *Tetrahedron Lett.*, 1989, **30**, 6573; (b) Y. Terao, M. Aono, and K. Achiwa, *Heterocycles*, 1988, **27**, 981; (c) R. Grigg, *Chem. Soc. Revs.*, 1987, **16**, 89; (d) E. Vedejs and F.G. West, *Chem. Rev.*, 1986, **86**, 941; (e) G. Stuckwisch, *Synthesis*, 1973, 469.
2. R. Smith and T. Livinghouse, *Tetrahedron*, 1985, **41**, 3559; O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997.
3. (a) R.C.F. Jones and S.C. Hirst, *Tetrahedron Lett.*, 1989, **30**, 5365; (b) *ibid.*, p.5361; (c) R.C.F. Jones and M.J. Smallridge, *Tetrahedron Lett.*, 1988, **29**, 5005.
4. See, e.g.: R.H. Barbour and D.J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1129.
5. T.F. Gallagher and J.L. Adams, *Tetrahedron Lett.*, 1989, **30**, 6599.
6. Prepared from N-benzyl-1,2-diaminoethane and triethyl orthoformate (4 mol. equiv.; p-TsOH, 0.05 mol. equiv.; 72%).
7. 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.
8. This suggests these additions are dipole-HO controlled (R. Sustmann, *Tetrahedron Lett.*, 1971, 2717).
9. K.N. Houk, J. Sims, C.R. Watts, and L.J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301; I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions,' Wiley, London, 1977, p.148.
10. This reaction stereochemistry can be rationalised by assuming the *anti* conformation (i) of the dipole and an endo transition state (cf. ref. 1c). The failure to observe n.O.e. enhancements involving C-5(H) leaves open the possibility of the opposite configuration at C-5.



(I)

11. E. Vedejs, S. Larsen, and F.G. West, *J. Org. Chem.*, 1985, **50**, 2170.
12. Removal of the pendant chain at N-1 should be possible *via* chemistry we have developed in the tetrahydropyridine series (ref. 3a), to access 2,4-disubstituted pyrroles.
13. Related eliminations from the products of azomethine ylide cycloaddition have been reported, e.g. refs. 1a,d.

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