Tetrahedron Letters Vol. 21, pp 885 - 888
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0040-4039/80/0222-0885$02.00/0

# STEREOSPECIFIC FORMATION OF AMIDINES BY 1,1-ADDITION OF AMINES TO ISOCYANIDES

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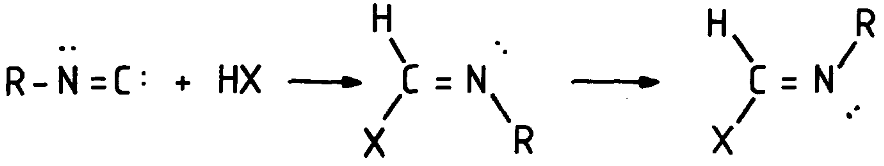
Summary. Addition of secondary amines to isonitriles in the presence of AgCl at low temperature gives isolable but thermodynamically unstable Z-amidines; only the more stable 6E undergoes ring expansion to the imidazoline 7.

1,1-Addition of reactive hydrogen compounds, HX, to isocyanides 1 can be used as a general route to the formation of substituted imines 2.[1] The reaction is however very slow when HX is a weak acid, e.g. with thiols, amines, alcohols, but can be successfully catalysed by compounds of Group IB and IIB metals.[2]

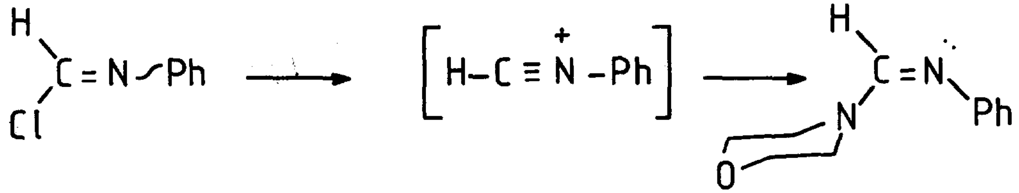


1 2Z 2E

We have now found that with AgCl as catalyst and in the absence of solvent (or in concentrated methylene chloride solution), addition of secondary amines proceeds at temperatures < 0° to give a single isomer (2Z) stereospecifically. The amidine isomer formed (2, X = $R_2N$-) which is now observed for the first time, is the thermodynamically less stable and on heating above room temperature or in the presence of acid, rapid and complete isomerisation to 2E occurs.

The isomer initially formed was assigned to Z-configuration (2) as follows. The -N-$CH_2$- resonances for the morpholino adducts (2, R = m-$ClC_6H_4$, p-$NO_2C_6H_4$, $C_6H_5$ X = O N-) are shielded by 0.65 ppm in $CDCl_3$ in 2Z, relative to 2E (attributable to the effect of the adjacent aryl group R in 2Z). This signal shows a smaller shift for the Z isomer when measured in benzene relative to chloroform[3] (0.33 ppm for 2E, 0.15 ppm for 2Z, R = m-ClC$_6$H$_4$, X = O N-) due to the fact that the N-aryl group already "solvates" the group X in 2Z. Similar effects were noted in all of the other pairs of E and Z amidines prepared by this route (R = YC$_6$H$_4$ where Y = H, o-, m- or p-Cl, o- or p-NO$_2$; X = Me$_2$N-, Et$_2$N-, (CH$_2$)$_2$N-, (CH$_2$)$_5$N, (CH$_2$)$_4$N).[4]

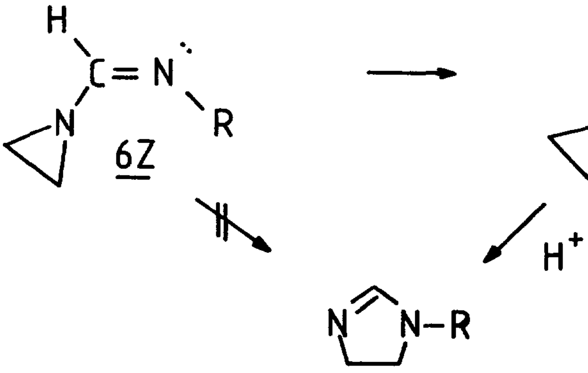
The configuration was confirmed chemically by the synthesis of the morphilino adduct by another route. Thus N-phenylformohydrazonyl chloride 3 was solvolysed in water in the presence of excess morpholine. Under these conditions the nitrilium ion 4 is formed



3 4 5

as an intermediate; reactions of nitrilium ions analogous to 4 have been shown[5] to invariably react with nucleophiles to give only the isomer in which the incoming nucleophile and the forming lone pair on the nitrogen are mutually *trans*. The product formed (5) in this case was identical (as shown by the n.m.r. and rate of conversion to the E isomer) to that formed initially by 1,1-addition of morpholine to the isocyanide in the presence of AgCl and again isomerisation (to the E form of 5) was observed on heating or in the presence of acid.

Addition of aziridine to 1 (in the presence of AgCl) at -10° gives an amidine 6Z which isomerises to 6E at 30°. However when a mixture of 6E and 6Z is treated with HCl an interesting ring expansion takes place with the formation of the imidazoline 7. However only the (more stable) E isomer of the amidine undergoes this reaction. This can be clearly seen by n.m.r.; when HCl is added to a mixture of 6Z and 6E (R = Ph) in chloroform at 34°, the -N-CH$_2$- resonance for 6Z (at $\delta$ 2.12 ppm) is quickly replaced by a larger resonance for 6E. This is followed by a slower disappearance of 6E which is converted to 7 (multiplet at 3.35-3.60 ppm).[6] With 6 (R = m-ClC$_6$H$_4$), which is a less nucleophilic amidine, addition of acid does not cause such a rapid isomerisation of 6Z to 6E and signals from all three materials are observed. It is clear again that the Z isomer formed kinetically does not undergo ring expansion directly but only subsequent to isomerisation to 6E. This establishes that the aziridine group and the amidine nitrogen



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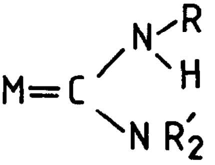
lone pair are *cis* in 6E, again confirming the structural assignment.

Because of the isolation of stable carbene complexes with, e.g. platinum,[7] it has been supposed that similar compounds (8) (as reactive intermediates) may be formed when amines are added to isonitriles in the presence of other catalysts. It is difficult



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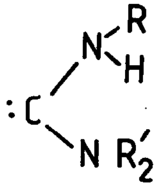

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however to visualise how a diamino carbene 9 (formed on dissociation of 8) would give the least stable amidine Z isomers stereospecifically. We therefore prefer a mechanism of formation of 2Z involving co-ordination of the isonitrile to $Ag^+$ (to give a pseudo nitrilium ion) followed by stereospecific attack by the amine and direct N→C proton transfer.

## References

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3. A similar method has been used to assign the structures of E and Z-aldimines: D.R. Boyd, C.G. Watson, W.B. Jennings and D.M. Jerina, J.C.S. Chem. Communs., 1972, 183.

4. A typical reaction procedure for **2Z** (X = $R_2N$) is as follows: the amine (0.1 mol), isonitrile (0.1 mol) and silver chloride (0.01 mol) were mixed at $-15^{\circ}$. Completion of reaction was indicated by the absence of characteristic isocyanide odour and $-N{\equiv}C$ stretching frequency in the i.r. The catalyst was removed by filtration and the residual amine removed in vacuo. The E isomer was prepared from this on reflux (6 h) in chloroform.

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(Received in UK 10 December 1979)