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Acid-catalysed ring-opening of *N*-(3,4-dihydro-4-oxoquinazolin-3-yl)-substituted aziridines: aziridine ring-opening with retention of configuration

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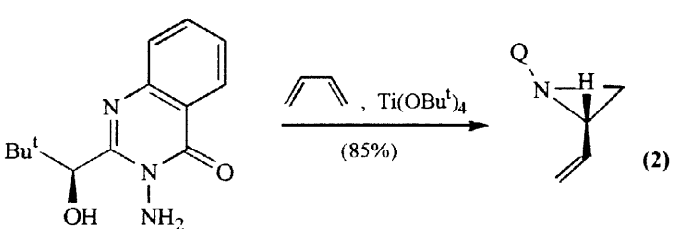
The presence of the quinazolin-4(3H)-one (Q) ring in 1-(Q)-2-vinylaziridine **(2)** can be used to control the stereochemistry of the 3-membered ring-opening; participation by the quinazolinone carbonyl oxygen brings about ring-opening with retention of configuration.

The chemistry of aziridines is of considerable interest since they are substrates for conversion to a range of biologically active molecules such as alkaloids, β-lactam antibiotics and α- or β-aminoacids.[1] However, few general methods are available for direct aziridination of alkenes and even fewer are completely stereoselective. Even where single enantiomers of these 3-membered rings are available, ring-opening reactions on them with C–N bond cleavage may not be completely selective in both regio- and stereo-senses. In principle, the aziridine *N*-substituent might be used to control this selectivity. In practice, however, the nature of this *N*-substituent is usually dictated by the aziridination method used[2,3] or by the requirement for it to be strongly electron-withdrawing (usually $-SO_2Ar$) to facilitate ring opening of the aziridine by nucleophiles, *e.g.* cuprates.[4]

We have previously described the preparation of a range of aziridines as single (enantiopure) diastereoisomers *via* reagent-controlled diastereoselective aziridination of alkenes using 3-acetoxyaminoquinazolinones *e.g.* **(1)** (Scheme 1).[5] The availability of these enantiopure aziridines has led us to examine the regio- and stereo-chemistry of their ring-opening. It was of particular interest to discover useful roles which the quinazolinone ring might play in this ring-opening before its eventual removal[6] thus allowing retrieval of only the chiral centres created in the aziridination.[7]



≡QNHOAc **(1)**

d.r. > 50 : 1

Scheme 1

Ring opening of aziridine **(2)** with sulphuric acid results in a 3:1 mixture of diol stereoisomers **(3)** and **(4)** (Scheme 2).[8]

Reaction of aziridine **(2)** with glacial acetic acid at 70 °C overnight gave two products (Scheme 2); di-acetate **(5)** and mono-acetate **(6)**. The stereostructures of di-acetate **(5)**, mono-acetate **(6)**, and the two diastereoisomeric diols **(3)** and **(4)** were interrelated and identified by the chemical correlation in Scheme 2 together with an X-ray crystal structure determination on di-acetate **(5)** (Fig.).[9] Thus di-acetate **(5)** and the major diol **(3)** are formed with inversion of configuration and **(6)** is formed with retention of configuration.[10]

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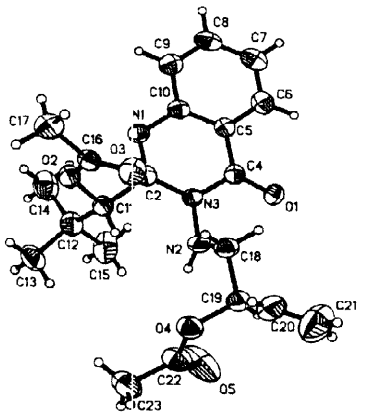
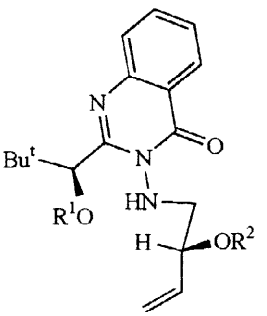
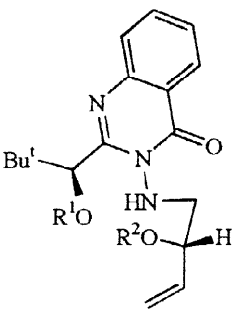
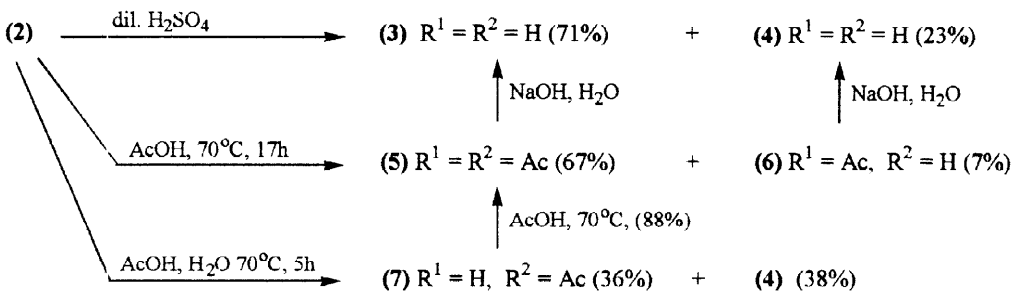


Fig. Molecular structure of one of the unique molecules of **(5)** showing 30% displacement ellipsoids.



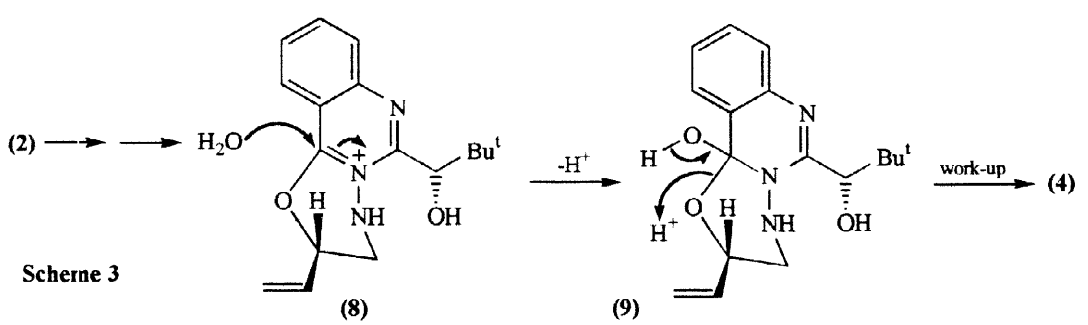




Scheme 2

Reaction of aziridine **(2)** with glacial acetic acid containing water (20 eq) and for a shorter time (5h) resulted in direct formation of diol **(4)** (38%) together with allylic mono-acetate **(7)** (36%), *i.e.* acetylation of the side-chain hydroxy group occurs subsequent to the aziridine ring-opening. Further treatment of this allylic mono-acetate **(7)** with the acetic acid-water solution above yielded di-acetate **(5)** showing that mono-acetate **(6)** was not formed from **(7)** *in situ*.

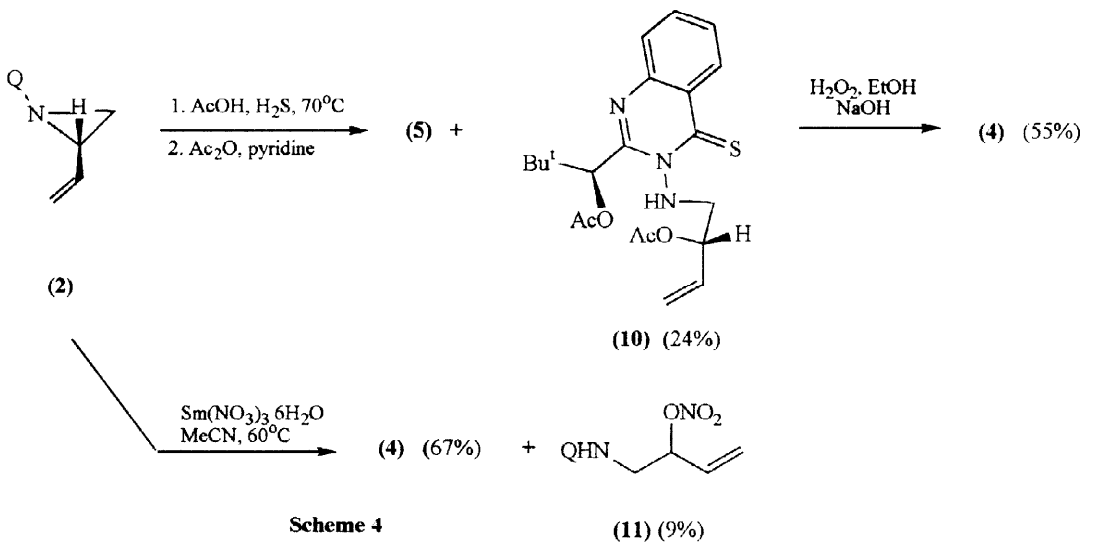
A mechanism consistent with the formation of diol **(4)** and hence mono-acetate **(6)** involves participation by the quinazolinone ring and is outlined in Scheme 3. A point of particular interest in this mechanism is that ring-opening of aziridine **(2)** and formation of intermediate **(8)** presumably must involve formation of an allylic cation at C-2 of the aziridine ring which is then attacked specifically from the *syn* face by the quinazolinone carbonyl oxygen. Heating the mixture in which diol **(4)** is formed for the longer time in acetic acid (Scheme 2) brings about acetylation of the hydroxy group in the quinazolinone side-chain but not of the less hindered allylic hydroxy group. We assume this is because the allylic hydroxy group is liberated from a cyclic amide acetal **(9)** only in the aqueous work-up.



Scheme 3

Participation by the quinazolinone in Scheme 3 would result in exchange of the C-4 carbonyl oxygen by oxygen from water in the formation of diol **(4)** and carrying out the reaction in the presence of hydrogen sulphide, therefore, should result in exchange of sulphur for this carbonyl oxygen. Heating the vinylaziridine **(2)** in acetic acid containing hydrogen sulphide and acetylation of the crude product gave a mixture of di-acetate **(5)** (50%) and the quinazolin-4-thione-substituted di-acetate **(10)** (24%) (Scheme 4). As expected, this di-acetate **(10)** is formed with retention of configuration as shown by conversion to the quinazolin-4-one-substituted diol **(4)** by treatment with basic hydrogen peroxide. Isolation of di-acetate **(5)** in Scheme 4 serves as an internal control and excludes the possibility of sulphur exchange for oxygen in allylic alcohol **(6)** under the reaction conditions as the route to thione **(10)**.

Conversion of aziridine **(2)** into diol **(4)** in higher yield (67%) can be accomplished by treatment with samarium nitrate hydrate in acetonitrile in 67% yield (Scheme 4); a minor product in this reaction is the allylic nitrate ester **(11)** (of unknown relative configuration). Participation by the quinazolinone ring may also be involved in this reaction.



Scheme 4

Ring-opening of aziridine **(2)** in Scheme 2 in the presence of molecular sieves to scavenge water gave a ratio of di-acetate **(5)** to mono-acetate **(6)** of 38:1. Since the pure di-acetate **(5)** is efficiently converted into allylic alcohol **(3)** (Scheme 2) by hydrolysis, methods for ring-opening of aziridine **(2)** to the corresponding allylic alcohol either with inversion or with retention of configuration are available.

Thus the quinazolinone *N*-substituent on aziridines resulting from completely diastereoselective reactions of 3-acetoxyaminoquinazolinones with alkenes can be further utilised in controlling the stereochemistry of aziridine ring-opening. We are currently investigating how this quinazolinone ring can be used to control the regiochemistry of aziridine ring-opening.

Acknowledgements

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7. R. S. Atkinson, A. P. Ayscough, W. T. Gattrell and T. M. Raynham, *Tetrahedron Lett.*, 1998, **39**, 497.
8. Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported in this paper.
9. **Crystal data** for **(5)**: $C_{11}H_{27}N_3O_5$, M = 401.46, monoclinic, space group $P2_1$, a = 11.033(4), b = 17.424(4), c = 11.899(2) Å; β = 103.84(2)°, V = 2221.0(10) Å^3, Z = 4, Dc = 1.201 Mg m^{-3}, F(000) = 856, μ = 0.086 mm^{-3}, λ(Mo-Kα) = 0.7107 Å.

   The crystal used for data collection was a colourless block with the approximate dimensions 0.64 × 0.53 × 0.43 mm. Unit cell parameters were determined by least squares refinement of the optimised setting angles of 26 reflections in the range $5.2 < \theta < 12.4°$. Intensity data for 3728 reflections were measured on a Siemens P4 diffractometer at 290K using an ω scan method. The reflections were corrected for Lorentz and polarisation effects to yield 3433 independent reflections (R_{int} = 0.008). The structure was solved by direct methods using the program SHELDTL–pc [G. M. Sheldrick, SHELXTL–pc Release 4.2, Siemens Analytical X-ray Instruments, Madison, WI, 1991] and refined by full-matrix least squares on F^2 using the program SHELXL93 [G. M. Sheldrick, SHELXL–93, Program for Crystal Structure Refinement, University of Göttingen, 1993]. Two unique and approximately superimposable molecules were found in the unit cell. Hydrogen atoms were included in calculated positions (C–H = 0.96 Å) with isotropic displacement parameters set to 1.2Ueq of the bonded atom. All non-hydrogen atoms were refined with anisotropic displacement parameters.

   Final cycles of refinement gave $R1 = 0.0457$, $wR2 = 0.1263$ for all data, $R1 = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$, $wR2 = [\Sigma w(Fo^2 - Fc^2)^2 / \Sigma w(Fo^2)^2]^{1/2}$, $w = 1/[\sigma^2(Fo^2) + (0.0691P)^2 + 0.46P]$ and $P = [\max(Fo^2, 0) + 2Fc^2]/3$. The maximum and minimum electron densities in the final ΔF map were 0.27 and –0.21 e Å^{-3}.
10. Compare K. Hori, T. Nishiguchi and A. Nabeya, *J. Org. Chem.*, 1997, **62**, 3081.