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Ring-opening of chiral *N*-(3,4-dihydro-4-oxoquinazolin-3-yl)-substituted aziridines (Q*-substituted aziridines): access to Q*-free chirons

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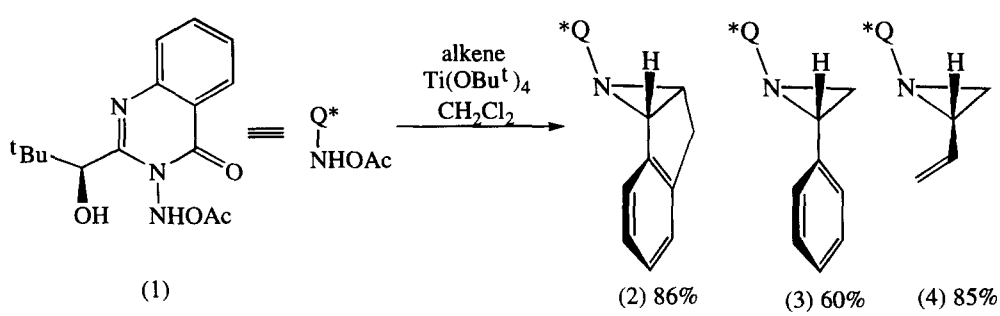
Abstract: The presence of the quinazolin-4(3H)-one ring (Q*) in *N*-(Q*)-aziridines facilitates ring-opening by nucleophiles: removal of the Q* group from enantiopure ring-opened products gives useful chirons.

3-Acetoxyaminoquinazolinones *e.g.* **1** are efficient aziridinating agents for alkenes.[1] Incorporation of a chiral centre into the substituent at the 2-position of the quinazolinone ring can result in high or even complete (reagent-controlled) diastereoselectivity in aziridination of a range of alkenes from styrene to α,β-unsaturated esters.[2,3] Thus aziridination of indene, styrene or butadiene by the *tert*-leucine-derived Q*NHOAc **1** in the presence of titanium(IV) *tert*-butoxide gives the corresponding aziridines **2**, **3** and **4** respectively (Scheme 1) in good yields and with diastereoselectivities >50 : 1 in every case.[2] The availability of these enantiopure aziridines lead us to examine the feasibility of their regio- and stereo-specific ring-opening since *N*-*N* bond cleavage of the ring-opened derivatives would then provide access to a range of enantiopure chirons.



(1) (2) 86% (3) 60% (4) 85%

Scheme 1

Ring-opening of aziridines in general requires stabilisation of the developing negative charge on nitrogen, most simply by prior coordination of the nitrogen lone pair by a proton or Lewis acid.[4] Alternatively, a strong electron-withdrawing substituent on nitrogen can be used (SO_2R,[5] CO_2R,[6] Ph_2PO[7]) in the absence of a proton source with the advantage that ring-opening with carbon nucleophiles, *e.g.* cuprates is feasible. The preferred

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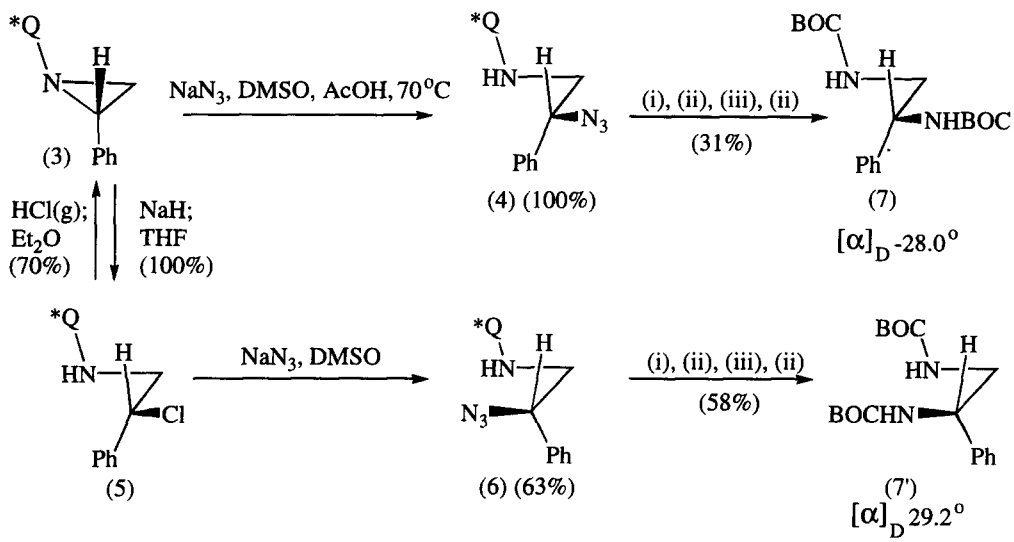
electron-withdrawing group for this purpose is the arylsulphonyl and highly enantioselective routes to aziridines bearing this *N*-substituent have been devised.[8] However, the severe acid conditions required for removal of the arylsulphonyl group from nitrogen in the ring-opened products limit its wider use.

We find that the quinazolinone ring as a substituent on the aziridine ring nitrogen in **2**–**4** is sufficiently electron-withdrawing to allow ring-opening by nucleophiles without the necessity for prior protonation of the ring nitrogen. Thus, heating the styrene-derived aziridine **3** with sodium azide in dimethylsulphoxide (Scheme 2) gave a mixture of products from which the azide **4** was isolated but in only 9% yield. However, inclusion of acetic acid (1 equiv.) in the reaction mixture gave this azide **4** as the only observed product (~100%). We assume that the function of the acetic acid is to protonate the anionic nitrogen after the rate-determining ring-opening step since the effect of the presence of acetic acid in Scheme 2 on the rate of disappearance of starting aziridine **3** was small. An S_N2-type ring-opening of aziridine **3** in Scheme 2 is likely since the azide **6**, prepared as shown in Scheme 2, was not identical to azide **4** from comparison of their NMR spectra. That ring-opening with hydrogen chloride in Scheme 2 takes place, as expected, with inversion of configuration was shown by re-conversion of chloride **5** back to aziridine **3** by base treatment.[9]

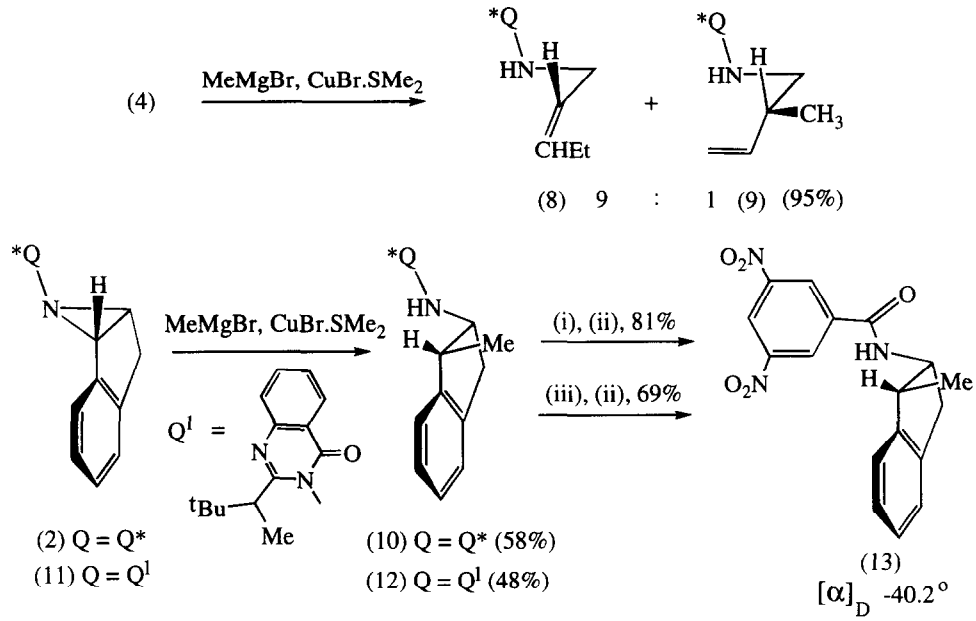


Reagents: (i) Pd/C, H_2, (ii) BOCN=C(Ph)CN, (iii) SmI_2, Bu^tOH, THF

Scheme 2

Azides **4** and **6** were diastereoisomerically pure and were converted to the corresponding BOC-protected 1,2-diamines **7** and **7′** by the reagents indicated in Scheme 2. The absolute configurations assigned to these enantiomers follow from the known absolute configuration of aziridine **3**[2] and from the stereochemistry in Scheme 2.

Aziridine **4** is opened by methyl magnesium bromide in the presence of copper bromide-dimethylsulphide to give a 9:1 mixture of S_N2' and S_N2 ring-opened products, **8** and **9** respectively, in almost quantitative yield. However, aziridine **2** is ring-opened by the same reagents to give amine **10** as a single diastereoisomer (Scheme 3).



Reagents: (i) SmI_2(xs), Bu^tOH, THF, (ii) 3,5-dinitrobenzoyl chloride
(iii) SmI_2 (0.5 equiv.), Mg (xs), Bu^tOH, THF

Scheme 3

Co-ordination of the aziridine ring nitrogen with a magnesium alkoxide formed in the reaction from the quinazolinone 2-substituent's hydroxy group is not important since reaction of aziridine **11**[10] under the same conditions gave an analogous ring-opened product **12**, albeit in lower yield (48%).[11] An X-ray structure determination of **12** (Fig. 1) shows that ring-opening takes place, as expected, with inversion of configuration.[12]

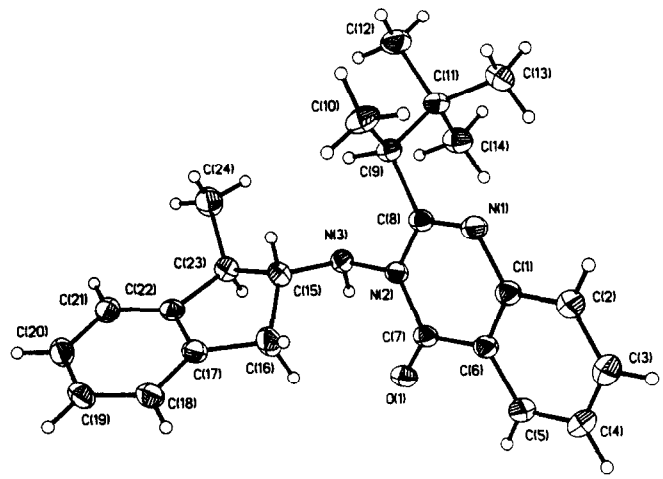


Fig. 1. ORTEP view of **12** (thermal ellipsoids are drawn at 50% probability level)

As shown in Scheme 3, reductive removal of the Q* group from ring-opened product **10** was accomplished in high yield using samarium(II) iodide[13] to give the amine, isolated as its 3,5-dinitrobenzoate **13**. Endo and co-

workers[14] have shown that reductions using samarium(II) diiodide can be made catalytic in Sm(II) by reduction of Sm(III) back to Sm(II) *in situ* by magnesium. We find that cleavage of Q* from ring-opened product **10** can also be accomplished using a sub-molar quantity of Sm(II) iodide in the presence of activated magnesium with only a small loss in yield of **13** (Scheme 3).

Thus the quinazolinone ring in 3-acetoxyaminoquinazolinones not only allows diastereoselective aziridination of alkenes by means of a chiral substituent in its 2-position but activates the aziridine ring towards opening by nucleophiles. Removal of the quinazolinone from these ring-opened products provides useful chirons as exemplified by the formation of **7**, **7'** and **13**.

Acknowledgements

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9. Analogous ring-opening reactions to those in Scheme 2 have been carried out using aziridine **3**.
10. Prepared as a single racemic diastereoisomer from indene and the corresponding 3-acetoxyamino-quinazolinone (Ulukanli, S., unpublished work).
11. The possibility of chelation by the quinazolinone oxygen with magnesium, and hence assistance in the ring-opening, cannot be excluded.
12. For structure **12**: *Crystal Data:* $C_{24}H_{29}N_3O_1$, M = 375.50, triclinic, space group $P\bar{1}$, a = 10.2760(7), b = 10.3681(7), c = 10.8949(8) Å; α = 77.910(1), β = 84.336(1), γ = 66.050(1)°, U = 1037.18(13)Å^3, Z = 2, D_c = 1.202 g cm^{-1}, μ = 0.074 mm^{-1} (Mo-Kα, λ = 0.71073 Å), *F(000)* = 404, T = 123(1) K., crystal size 0.25 × 0.30 × 0.50 mm, 5867 reflections measured, 4114 unique, (R_{int} = 0.0140). Unit cell determination and data were collected on a Siemens SMART CCD area-detector diffractometer. The data collection nominally covered a hemisphere of reciprocal space by a combination of three sets of exposures; each set had a different ϕ angle for the crystal and each exposure covered 0.3° in ω. The crystal-to-detector distance was 4.92 cm. Coverage of the unique set is over 94% complete to at least 24.7° in θ. Crystal decay was monitored by repeating the first 50 frames at the end of the data collection and analysing the duplicate reflections. The crystal was cooled with an Oxford Cryostream Cooler (Cosier, J. and Glazer, A. M., *J. Appl. Crystallogr.*, **1986**, *19*, 105). Structure solution by direct methods, full-matrix least-squares refinement on F^2 with weighting $w^{-1} = \sigma^2(F_o^2) + (0.0712P)^2 + 0.1560P$, where $P = (F_o^2 + 2F_c^2)/3$, anisotropic displacement parameters. riding hydrogen atoms, no absorption correction gave at convergence, (Δ/σ_{max} 0.001), $Rw = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ = 0.1234 for all data, conventional R = 0.0437 on F values of 3348 reflections with $I > 2\sigma(I)$, S = 1.054 for all data and 254 parameters. Final difference map between +0.25 and -0.21 e Å^{-3}. Programs: Siemens SMART and SAINT control and integration software, SHELXTL (Sheldrick, G.M., University of Göttingen, Germany). Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.
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