Aziridination of naphthalene by 3-acetoxyaminoquinazolin-4(3*H*)-ones

Robert S. Atkinson,*[a]† Emma Barker,[a] Christopher K. Meades[a] and Hassan A. Albar*[b]‡

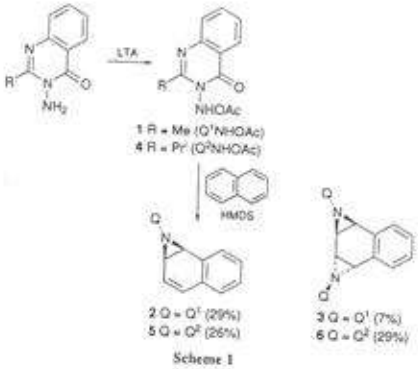
[a] *Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH*
[b] *Department of Chemistry, King Abdul Aziz University, Jeddah 21413, Saudi Arabia*

Reaction of naphthalene with 3-acetoxyaminoquinazolin-ones 1, 4 or 8 in the presence of hexamethyldisilazane gives the corresponding mono-aziridine as the major (for 1) or exclusive (for 8) product; on heating in benzene, aziridine 5 acts as an aziridinating agent for alkenes.

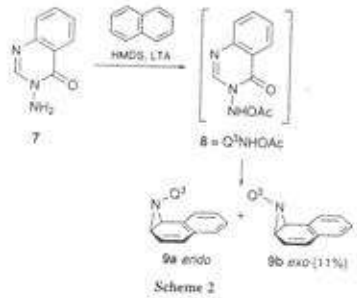
Intermolecular non-enzymic reactions of simple naphthalenes which result in exclusive 1,2-addition to a peripheral double bond are uncommon: the remaining 3,4-double bond in the functionalised six-membered ring will usually be more reactive than any bond in the parent naphthalene with the result that bis-addition (1,2 and 3,4) is the major pathway. Thus the reaction of naphthalene with *m*-chloroperoxybenzoic acid[1] or with methyl-(trifluoromethyl)dioxirane[2] is reported to give the *trans*-1,2,3,4-bis-epoxide but none of the mono-epoxide. A stereo-selective addition to just one double bond would be valuable because subsequent stereoselective addition to the second double bond, using a different reagent, would lead to 1,2,3,4-tetrahydronaphthalene derivatives as single diastereoisomers.

Aziridination of naphthalene (3 equiv.) with 3-acetoxy-amino-2-methylquinazolinone **1** (Q^1NHOAc)[3] in the presence of hexamethyldisilazane (HMDS) (3 equiv.) in chloroform gave mono-aziridine **2** (29%) and bis-aziridine **3** (7%) from examination of the crude reaction product by NMR spectroscopy using triphenylmethane as an internal standard (Scheme 1).§ After removal of the bulk of the naphthalene by sublimation (40 °C, $\sim 10^{-3}$ mmHg), the products **2** and **3** were isolated in 17 and 3% yields respectively after chromatography on de-activated silica.

When aziridination of naphthalene was carried out using 3-acetoxyamino-2-isopropylquinazolinone **4** (Q^2NHOAc)[4] under the same conditions, the analogous mono- and bis-aziridines **5** and **6** were present in 26 and 29% yields in the crude reaction product and isolated in 20 and 11% yields respectively (Scheme 1) after chromatography as described above.



Scheme 1

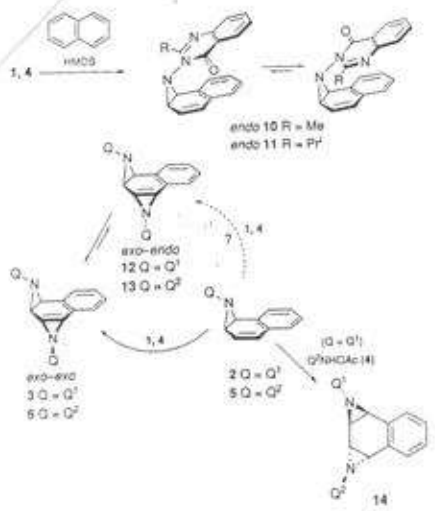


Scheme 2

The presumed 3-acetoxyaminoquinazolinone **8** (Q^3NHOAc) (Scheme 2), unsubstituted in the 2-position, is not stable under the conditions used for the preparation of Q^1NHOAc **1** and Q^2NHOAc **4**. However, *N*-acetoxylation of the corresponding 3-aminoquinazolinone **7** by lead tetraacetate (LTA) in the presence of naphthalene (3 equiv.) and HMDS (3 equiv.) gave the mono-aziridine, isolated as a mixture of *N*-invertomers **9a** (*endo*) and **9b** (*exo*) (11%) after chromatography: examination of the crude reaction product revealed that no bis-aziridine was formed.

Following the course of these aziridinations by NMR spectroscopy at temperatures from −20 °C to ambient is particularly informative and the changes observed can be interpreted as follows (Scheme 3): (a) the kinetically-formed products in each case are, as expected,[3] the *endo*-*N*-invertomers **10** and **11** (Scheme 3) and **9a** (Scheme 2) in which the quinazolinone ring and naphthalene residue are *cis*; (b) for each of the *endo*-invertomers **10** and **11** two *rotamers* around the *N*–*N* bond are present (ratio 3:1 and 5:1 respectively): only a single rotamer appears to be present in the case of **9a**; (c) interconversion between the *N*–*N* bond rotamers in **10** and **11** although slow on the NMR time-scale is fast on the *N*-inversion (*endo*→*exo*) time-scale;¶ (d) bis-aziridines **3** and **6** have the *exo*–*exo* configuration;‖ if the corresponding *exo*–*endo* stereo-isomers **12** and **13** are intermediates in the formation of **3** and **6**, their concentrations are not sufficiently high for detection; (e) signals for mono-aziridines **2** and **5** (*exo*-invertomers) only become significant in these NMR spectra when signals from the respective aziridinating agents Q^1NHOAc **1** or Q^2NHOAc **4** have almost disappeared;** (f) bis-aziridination takes place predominantly or exclusively from the *exo*-invertomers **2** and **5**.

The competitive or predominant formation of mono-aziridine in these reactions arises as a consequence of (f) above together with a slow rate of *N*-inversion (*endo*→*exo*) for the mono-aziridine. Support for the conclusion in (f) comes from the absence of bis-aziridine as a product from the reaction in Scheme 2 and from the greater ratio of mono-:bis-aziridines **2**:**3** over **5**:**6**. The rates of *N*-inversion (*endo*→*exo*) in these mono-aziridines would be expected to increase in the order **9a** < **10** < **11** and this order correlates with the ratios bis-:mono-

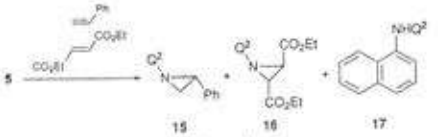


Scheme 3

aziridine obtained. The absence of any bis-aziridine in the reaction in Scheme 2 is because reaction of Q^1NHOAc with naphthalene is complete, and gives only *endo*-invertomer **9a**, before conversion of **9a** to **9b** takes place as the temperature is raised to ambient.††

syn-Addition of these 3-acetoxyaminoquinazolinones to aryl-substituted double bonds to give *endo*-substituted aziridines as kinetically-formed products is well known and has been ascribed to an attractive interaction between the quinazolinone and aryl rings in the transition state.[3] Deactivation of the residual 3,4-double bond in the *endo*-configured mono-aziridines **10**, **11** and **9a** presumably arises from a similar interaction in these stereoisomers in which the aziridine ring bonds are now fully formed.

Further functionalisation of the 3,4-double bond in these mono-aziridines is under study: the mono-aziridine **2** reacts with Q^2NHOAc **4** (2 equiv.) to give the bis-aziridine **14** in 68% yield.



Scheme 4

Heating aziridine **5** in benzene containing a mixture of styrene (3 equiv.) and diethyl fumarate (3 equiv.) gave the corresponding aziridines **15** and **16** and the amine **17** in a 1 : 1 : 2 ratio (Scheme 4). It is likely that the intermediate in this aziridination is the nitrene [Q^2N:] since the same selectivity for these two alkenes is found for this species generated by other means.[5]

Footnotes and References

† E-mail: vow@le.ac.uk
‡ E-mail: scf30436@kaau.edu.sa

§ In the absence of HMDS, the major product is 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)aminonaphthalene **17** (22%).

¶ As the reactions proceed the concentrations of **10** and **11** are reduced to zero but there is no change in the ratios of their two rotamers.

‖ The two aziridine rings in these bis-aziridines would be expected to be *trans*-disposed based on steric grounds and this assignment is supported by the C_{2v} symmetry present (NMR spectroscopy) in the corresponding bis-aziridine obtained from reaction of naphthalene and 3-acetoxyamino-2-[(1′*S*)-2′,2′-dimethyl-1′-hydroxypropyl]quinazolin-4(3*H*)-one (see R. S. Atkinson, A. P. Ayscough, W. T. Gattrell and T. M. Raynham, *Chem. Commun.*, 1996, 1935).

** The rates of aziridination of *exo*-*N*-invertomers **2** and **5** by Q^1NHOAc **1** and Q^2NHOAc **4** are expected to be faster than that of naphthalene.

†† Further support for the conclusion in (f) is the higher ratio mono-: bis-aziridine 5 : 6 (4 : 1) obtained using the nitrene [Q^2N:] derived from Q^2NHOAc **4** and triethylamine (ref. 5): aziridinations of alkenes using [Q^2N:] take place at slightly lower temperatures than those using Q^1NHOAc.

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