Aziridination of Alkenes using 3-Acetoxyaminoquinazolin-4-(3*H*)ones in the Presence of Tertiary Amines: Evidence for an Azaimide (*N*-Nitrene) Intermediate

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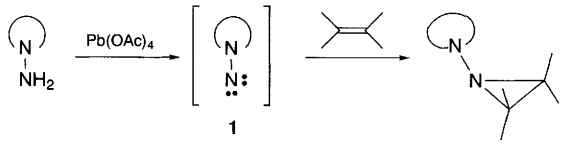
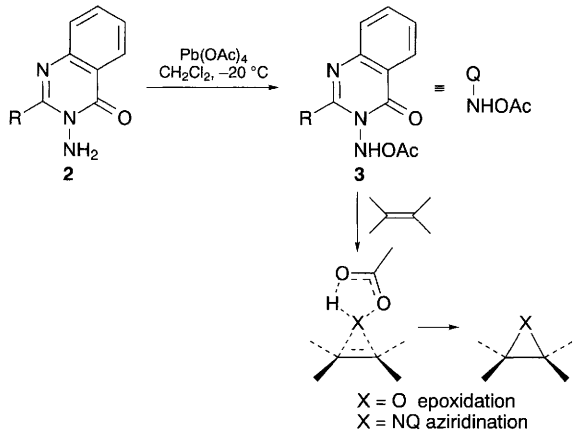
Solutions of the triethylammonium imide **8**, formed from triethylamine and 3-acetoxyaminoquinazolinone **4**, react with alkenes at −30 °C to give aziridines; the reactivity of the aziridinating intermediate is consistent with its formulation as an azaimide (*N*-nitrene).

Oxidation of certain heterocyclic *N*-amino compounds with lead tetraacetate (LTA) in the presence of alkenes gives aziridines[1] (Scheme 1).



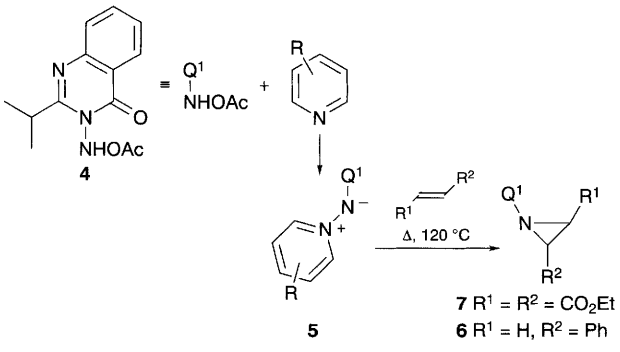
Scheme 1

The reactive intermediates in these aziridinations were thought to be *N*-nitrenes (azaimides) **1** but, at least for 2-substituted-3-aminoquinazolinones **2** (Scheme 2) are now known to be 3-acetoxyaminoquinazolinones **3**.[2] As a result, aziridination using **3** can be considered as the nitrogen analogue of epoxidation using peroxyacetic acid (Scheme 2) and both reactions have features in common.[3]



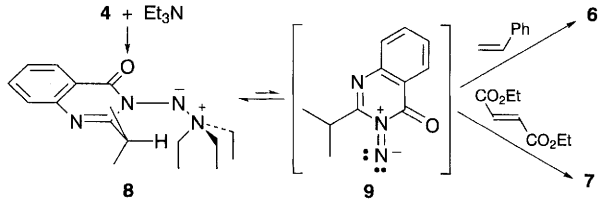
Scheme 2

The reaction of 3-acetoxyamino-2-isopropylquinazolinone (Q[1]NHOAc) **4** with pyridine and substituted pyridines gives rise to isolable pyridinium *N*-(quinazolinonyl) imides **5** whose thermal decomposition in alkenes (diethyl fumarate, styrene) at 120 °C also gives aziridines (Scheme 3).[4]



Scheme 3

We report that reaction of Q[1]NHOAc **4** with trialkylamines gives rise to unstable imides which bring about the aziridination of alkenes at below room temperature. Thus, addition of triethylamine (2 equiv.) to acetic acid-free solutions of Q[1]NHOAc **4** at −20 °C results in complete conversion to triethylammonium imide **8** (Scheme 4) analogous to **5**.



Scheme 4

The three methylene groups in the triethylammonium residue of **8** appear as two broad signals, each 3 protons at δ 3.45 and 3.82 in its NMR spectrum as a result of the Q[1]-N chiral axis which renders the protons in each of these equivalent methylene groups diastereoisotopic:[4] the methyl groups in the 2-isopropyl substituent are also diastereoisotopic.

Addition of styrene (3 equiv.) to solutions of imide **8** at −20 °C and then allowing to warm to room temp. gives aziridine **6** in 77% isolated yield. Similarly, addition of diethyl fumarate (3 equiv.) gives the corresponding aziridine **7** in 83% yield.†

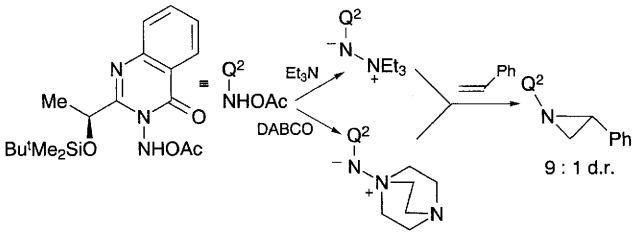
A number of experiments suggest that the species which brings about these aziridinations is not the imide **8** but the corresponding azaimide (*N*-nitrene) **9** (Scheme 4). Thus, a variety of other tertiary amines can be used in place of triethylamine to give the corresponding trialkylammonium imides including diazabicyclooctane (DABCO), quinine and *N*,*N*-dimethyl-*N*,α-methylbenzylamine. In each case, aziridination of a 1 : 1 mixture of diethyl fumarate and styrene using these imides gave the same ratio of aziridines **6** and **7** (1 : 1, respectively) showing that the reactivity of the aziridinating agent is independent of the nature of the tertiary amine. In the aziridinations of diethyl fumarate and styrene with the imides derived from the enantiopure amines, quinine and *N*,*N*-dimethyl-*N*,α-methylbenzylamine above, solutions of the product aziridines **6** and **7** were devoid of optical activity. This lack of asymmetric induction is also consistent with the absence of the chiral amine in the transition state of the alkene aziridination.

Kinetic studies using the reaction of triethylammonium imide **8** with styrene or with diethyl fumarate alone, showed the reactions are zero order in alkene, which also supports a mechanism involving formation of the azaimide **9** from the imide **8**.‡

Heating the pyridinium imide **5** (R = 2-Me) in boiling benzene containing a 1 : 1 mixture of diethyl fumarate and styrene also gave a similar ratio of aziridines **7** and **6** (1.1 : 1, respectively). It seems likely, therefore, that the same intermediate, the azaimide **9**, is involved in aziridinations using both trialkylammonium and pyridinium imides. By contrast, the Q[1]NHOAc **4** reacts (in the absence of tertiary amine) exclusively with styrene in a competition experiment using the 1 : 1 mixture of diethyl fumarate and styrene above.

Not only is the selectivity in these aziridinations, between two alkenes of very different electron demand, independent of

the nature of the trialkylammonium moiety of the imide but so also is the stereoselectivity in the use of an imide bearing a chiral 2-substituent on the quinazolinone and a prochiral alkene (Scheme 5).

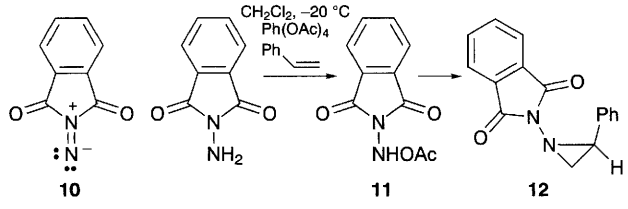


Scheme 5

Further support for the azaimide **5** as the aziridinating agent in reactions using the trialkylammonium imide above comes from analogy with aziridination of alkenes using azaimide **10** which is thought to be the common intermediate in thermal decomposition of a number of chemically different precursors.[5] In competitive experiments using a mixture of methyl acrylate and styrene, this azaimide **10** exhibited a greater preference for methyl acrylate than the presumed *N*-acetoxyaminophthalimide intermediate (see below) generated from *N*-aminophthalimide by oxidation with LTA, *i.e.* it is also more nucleophilic.

A comparative survey of the reactivity of 3-acetoxyaminoquinazolinone **4** and the corresponding azaimide **9** in aziridinations of alkenes reveals a remarkable similarity; both are stereospecific in their reactions with *Z*- and *E*-but-2-ene, both react with electron-rich and with electron-deficient alkenes (see above), both react stereoselectively *syn* with cyclohexenol. In some cases the stereoselectivity is higher in aziridinations using the azaimide (Scheme 5); in others (cyclohexenol) it is greater using the 3-acetoxyaminoquinazolinone (*ca.* 20 : 1 *vs.* 8 : 1).

In aziridination of *e.g.* styrene by oxidative addition of *N*-aminophthalimide in which *N*-acetoxyaminophthalimide **11** is believed to be the aziridinating agent,[2] the *Z*-invertomer of the aziridine **12** at nitrogen is the kinetically-formed product[6] (Scheme 6).



Scheme 6

Formation of the corresponding *Z*-invertomer as the kinetically formed product also occurs in aziridination of styrene using 3-acetoxyaminoquinazolinones **3** but because the rate of inversion at the aziridine ring nitrogen is faster with a quinazolinone as the *N*-substituent, it has not been possible to show experimentally that aziridination is completely *syn*-selective as is the case in Scheme 6.[2] Aziridination *via* the azaimide **9** proceeds at a sufficiently lower temperature for the application of NMR spectroscopy to reveal that not only is the kinetically formed product the *Z*-invertomer but also that this reaction is completely *syn*-stereoselective (>20 : 1).

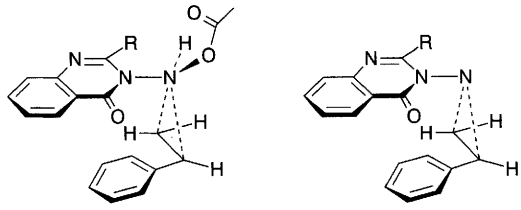


Fig. 1

The similar reactivity profile for the two aziridinating agents, the 3-acetoxyaminoquinazolinone **2** and the azaimide **9**, can be accounted for in terms of two similar transition states (Fig. 1). In both there is an attractive interaction between the quinazolinone carbonyl carbon and the phenyl ring of styrene which leads to the above *syn* selectivity.[6]

The stereoselective formation of the *Z*-aziridine in the reaction of azaimide **9** with cyclohexenol and the similarity in diastereoisomeric ratios from aziridination of acyclic allylic alcohols using azaimide **9** or Q^{1}NHOAc **4** is at first surprising. However, Adam and Nestler have shown[7] that using certain acyclic allyl alcohols, epoxidation using *m*-chloroperoxybenzoic acid and the ene reaction using singlet oxygen (*via* a perepoxide intermediate) show very similar diastereoselectivities. Since the azaimide **9** is isoelectronic at nitrogen with singlet oxygen at oxygen and since the Q^{1}NHOAc **4** is a nitrogen analogue of a peroxyacid, similar diastereoselectivities in their reactions with allylic alcohols is less surprising.

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Footnotes

† All new compounds in this paper have been fully characterised.
‡ The formation of azaimide **9** from imide **8** is assumed to be reversible.

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