3-Acetoxyamino-2-trifluoromethylquinazolin-4(3*H*)one as an Aziridinating Agent for Alkenes

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The title compound **4**, prepared by lead tetraacetate oxidation of **5**, is stable at room temperature and aziridinates alkenes in better yield and higher diastereoselectivity than, *e.g.* the 2-ethyl compound **1**; hydrazinolysis of the quinazolinone ring in **20** gives the corresponding *N*-aminoaziridine **21** in 64% yield.

Solutions of *N*-acetoxyaminoquinazolinones, *e.g.* **1**, are obtained by oxidation of the corresponding *N*-aminoquinazolinones **2** with lead tetraacetate at −20 °C.[1] Solutions of **1** are aziridinating agents for alkenes (Scheme 1) and may be regarded as nitrogen equivalents of peracids.[2]

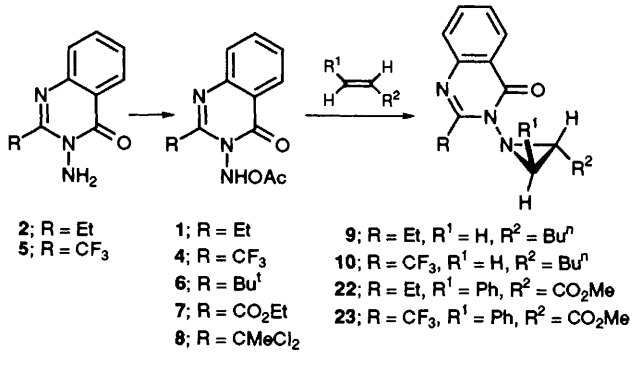
We have shown that when R in **2** is chiral, diastereoselective aziridination of prochiral alkenes occurs.[3] When the *N*-aminoquinazolinones in these reactions are used in enantiopure form, the corresponding *N*-acetoxyaminoquinazolinones may be regarded as synthetic equivalents of (chiral) NH_2^+ synthons since the aziridines may be ring-opened with protic acids and the N–N bond reductively cleaved.[4]

At temperatures >0 °C, decomposition of **1** occurs with the formation of the quinazolinone **3** (80%). Formation of **3** from **1** is competitive with aziridinations on using the latter reagent, and **3** is the major product in attempted aziridination of unreactive alkenes.

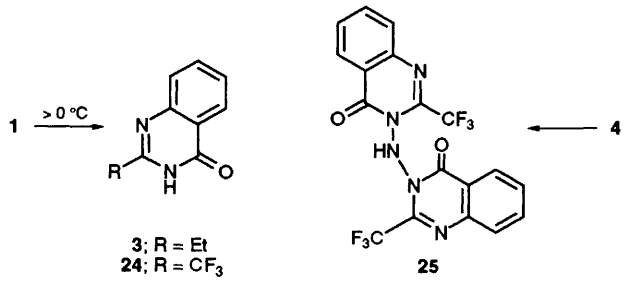
We find that the title compound **4**, prepared in the usual way by oxidation of **5**, is considerably more stable than **1** and all other *N*-acetoxyaminoquinazolinones that we have prepared to date, including **6–8**: **4** has been isolated as a crystalline solid in 67% yield and is stable at ambient temperature for several days.† More importantly, **4** gives superior yields of aziridines than do other *N*-acetoxyaminoquinazolinones, including **1** and **6–8**; in every case where yields of aziridines are poor using **1** they are improved using **4** or are comparable using **4** together with smaller excesses of alkene. For example, hex-1-ene (3 mol. equiv.) reacts with **1** to give the aziridine **9** in only 11% yield. Using **4** with only 1.2 equiv. of hex-1-ene and stirring in dichloromethane overnight gives a 51% isolated yield of the aziridine **10**.‡

Not only are yields in aziridinations using **4** improved but the stereoselectivity is also improved. Thus aziridination of cyclohexenol **11** with **1** gives *syn* **12** and *anti* **13** diastereoisomers in a 95:5 ratio.[2] Using **4**, only the analogous *syn*-diastereoisomer **14** was isolated (81% yield) and no signals from the *anti*-diastereoisomer **15** were visible in the NMR spectrum of the crude aziridination product.§ A sample of *anti*-diastereoisomer **15** became available when it was found that aziridination of **11** using **4** in the presence of aqueous sodium hydrogencarbonate solution (two-phase) gave both *syn*- and *anti*-aziridines **14** and **15** in a 1.3:1 ratio, which were separated by flash chromatography giving crystalline solids, m.p. 133–135 and 121–122 °C, respectively. Hydrogen bonding between the allylic hydroxy group and the aziridinating agent **4**, which delivers the aziridine on to the *syn*-face, appears to be disrupted under these latter conditions.

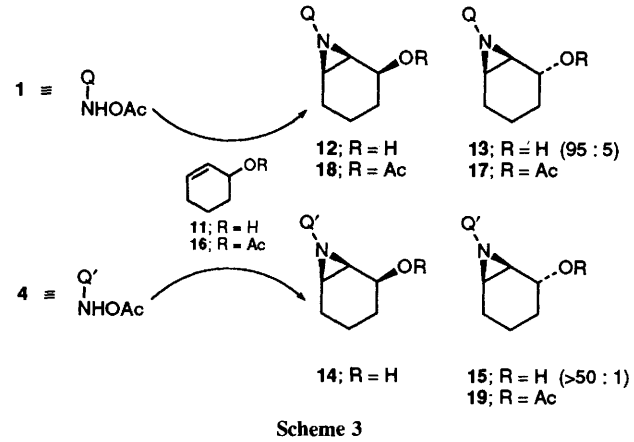
Aziridination of cyclohexenyl acetate **16** is completely *anti*-diastereoselective using **1** but the yield of **17** is poor (7%).[2] We have shown previously that yields in aziridinations of these less reactive alkenes can be increased by inclusion of trifluoroacetic acid (TFA) (3–6 mol equiv.) in the reaction mixture.[6] However, not only must the aziridine be stable to these acid conditions, but diastereoselectivity may be eroded. Thus, aziridination of the above cyclohexenyl acetate **16** (3 mol equiv.) with **1** in the presence of TFA (3 mol equiv.) proceeds in 66% yield but 1.2:1 mixture of aziridines **17** and **18** is produced. Aziridination of cyclohexenyl acetate (2 mol equiv.) using **4** in the absence of TFA gave only the



Scheme 1



Scheme 2

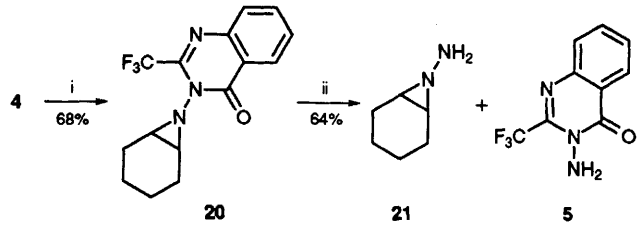


Scheme 3

† **CAUTION**: These *N*-acetoxyaminoquinazolinones are powerful electrophiles, which react avidly with amines and heterocyclic bases and should be handled with care.

‡ All compounds in this paper have been characterised by spectroscopic and elemental analysis.

§ Assignments of relative configuration in **14**, **15** and **19** followed by comparison of appropriate coupling constants in their NMR spectra with those of **12**, **13**, **17** and **18**.



Scheme 4 *Reagents and conditions*: i, cyclohexene (3 mol equiv.); ii, NH_2NH_2, 120 °C, 5 min

anti-diastereoisomer **19**, m.p. 130–132 °C in 32% isolated yield.

Aziridination of cyclohexene (3 mol equiv.) with **4** gave **20**, m.p. 127–128 °C (68%) (Scheme 4). As indicated in Scheme 4, the trifluoromethyl substituent activates the quinazolinone ring towards nucleophilic attack allowing its hydrazinolysis and isolation of *N*-aminoaziridine **21** (64%).

It has previously been shown by Eschenmoser *et al.*[6] that hydrazinolysis of *N*-phthalimidoaziridines analogous to **9** can be used as a route to *N*-aminoaziridines (including **21**) but the quinazolinone ring in **9** cannot be removed in this way.

A competitive reaction between **1** and **4** for a limited quantity of methyl cinnamate (0.5 mol equiv.) gave a *ca.* 1:1 ratio of aziridines **22** and **23** (Scheme 1) from NMR comparison of the spectrum of the crude reaction mixture with those of authentic samples. At least in this case, therefore, *N*-acetoxyaminoquinazolinone **4** is not intrinsically more reactive than **1** as an aziridinating agent.

The greater yields associated with the use of **4** arise from its slower decay by a pathway analogous to that by which **3** (Scheme 2) is formed. In fact the 2-trifluoromethyl analogue **24** is never recovered as a by-product in aziridinations using **4**. Instead a crystalline material, m.p. 178–179 °C, is isolated which is assigned the *N,N*-bis(oxoquinazolin-*N'*-yl)amine structure **25**.

The stability of **4** and its efficacy as an aziridinating agent should be of assistance in the design of a shelf-stable, chiral, quinazolinone-based aziridinating agent.[7]

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