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Diastereoselective aziridination of cyclic dienes with 3-acetoxyaminoquinazolin-4(3*H*)-ones: competitive formation of insertion products from cyclohexadienes

Robert S. Atkinson* and Christopher K. Meades

Department of Chemistry, Leicester University, Leicester LE1 7RH, UK

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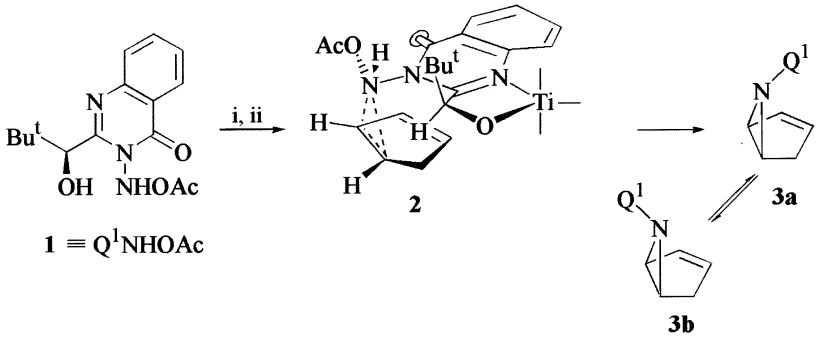
Abstract

Aziridination of cyclopentadiene and cycloheptadiene with 3-acetoxyamino-2-[(*S*)-1-hydroxy-2,2-dimethylpropyl]quinazolin-4(3*H*)-one **1** in the presence of titanium(IV) *tert*-butoxide gave the corresponding vinyl aziridines highly diastereoselectively: the corresponding aziridination product of cyclohexa-1,3-diene is formed less diastereoselectively and is accompanied by a by-product **9** from formal insertion into an allylic C–H bond, a previously unobserved reaction type for 3-acetoxyaminoquinazolinones.

3-Acetoxyaminoquinazolinones QNHOAc are versatile aziridinating agents for alkenes of widely different π-electron availability.[1] Reaction of cyclopentadiene with the enantiopure 3-acetoxyaminoquinazolinone **1** (Q^1NHOAc) (Scheme 1) in the presence of titanium(IV) *tert*butoxide[2] (TTB) gave the aziridine **3a** (25%) as a single diastereoisomer whose relative and therefore absolute configuration[3] was determined by X-ray crystallography (Fig. 1).[4]



1 ≡ Q^1NHOAc

Scheme 1. *Reagents*: (i) $Ti(OBu^t)_4$, CH_2Cl_2; (ii) cyclopentadiene

* Corresponding author.

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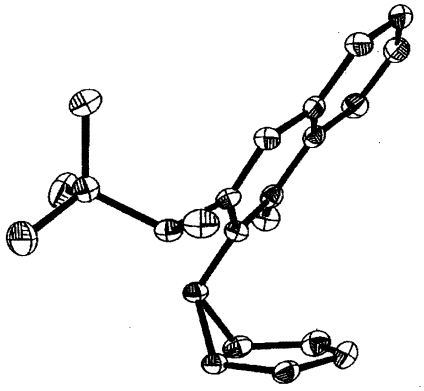
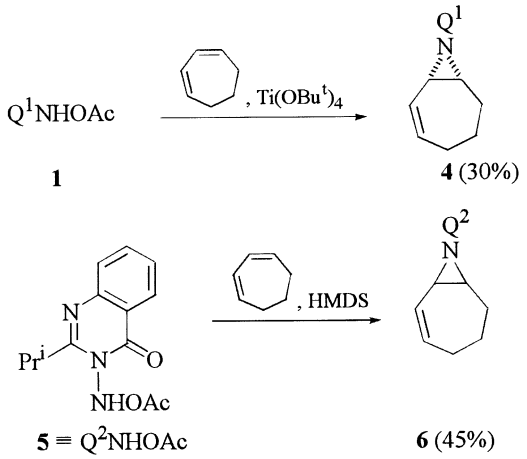


Figure 1. Molecular structure of **3a**. Displacement parameters are shown at the 30% probability level, H atoms are omitted for clarity

From the crystal structure of aziridine **3a** it is clear that the Q^1 group is *cis* to the cyclopentadiene ring residue. On heating at 60°C for 1 h, thermodynamic equilibration to give a 1:1 mixture of aziridine *N*-invertomers **3a** and **3b** occurs and accordingly **3a** is the expected kinetically-formed product.[1]

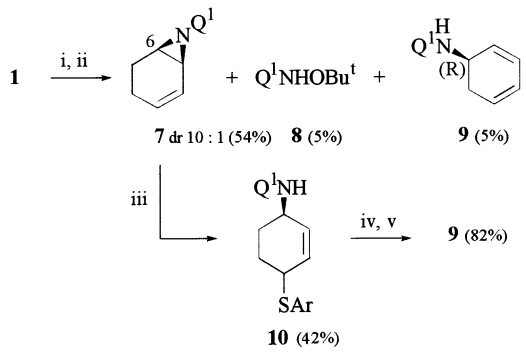
The sense of diastereoselectivity in formation of aziridine **3a** is consistent with a titanium-coordinated and chelated complex of Q^1NHOAc **1**, which undergoes reaction with the cyclopentadiene from the less-hindered face as in transition state ($ts^{\#}$) **2** (Scheme 1) with the expected *endo*-orientation of the cyclopentadiene giving rise to the *N*-invertomer **3a**.[2]

Reaction of cycloheptadiene with Q^1NHOAc **1** and TTB gave aziridine **4** (30%) as the major product whose NMR spectrum indicated that it was a single diastereoisomer[5] (Scheme 2). Reaction of the 2-isopropyl analogue **5** (Q^2NHOAc) with cycloheptadiene in the presence of HMDS[6] gave the corresponding aziridine **6** (45%).



Scheme 2.

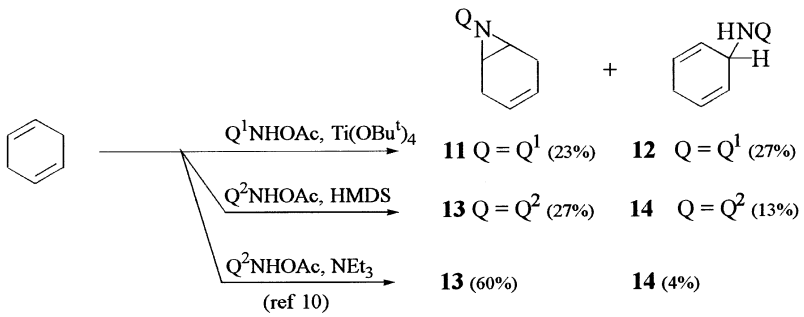
Reaction of cyclohexa-1,3-diene with Q^1NHOAc **1** and TTB gave both diastereoisomers of aziridine **7** (dr 10:1)[7] together with a mixture of *tert*-butoxyaminoquinazolinone **8**, (a known reaction product of Q^1NHOAc **1** with titanium(IV) *tert*-butoxide)[2] and dienylamine **9**, an apparent C–H insertion product of cyclohexa-1,3-diene (Scheme 3).



Scheme 3. *Reagents*: (i) $Ti(OBu^t)_4$; (ii) cyclohexa-1,3-diene (2 equiv.); (iii) *p*-ClC_6H_4SH, CH_2Cl_2, 90°C; (iv) H_2O_2–HOAc; (v) Δ, CCl_4

From its ^1H NMR spectrum, this dienylamine **9** appeared to be a single diastereoisomer and this conclusion was supported by analysis of the NMR spectrum of the product from Swern oxidation of the alcohol group in the quinazolinone 2-substituent followed by sodium borohydride reduction of the resulting ketone: the additional resonances were assignable to a new diastereoisomer of **9** (dr ~1:1). Chemical correlation between the major aziridine diastereoisomer **7** and dienylamine **9** was carried out (Scheme 3) by S_N2' ring-opening[8] of the aziridine **7** with *p*-chlorothiophenol to give arylsulfide **10** followed by thermolysis of the derived sulfoxide. Thus, the configuration at the cyclohexadienyl ring carbon in dienylamine **9** corresponds to that at C-6 in aziridine **7** and is *R*, assuming that aziridine **7** is formed by a ts[#] analogous to **2**.

A relatively larger proportion of insertion to aziridine product was obtained in the reaction of cyclohexa-1,4-diene with Q^1NHOAc and with Q^2NHOAc (Scheme 4).

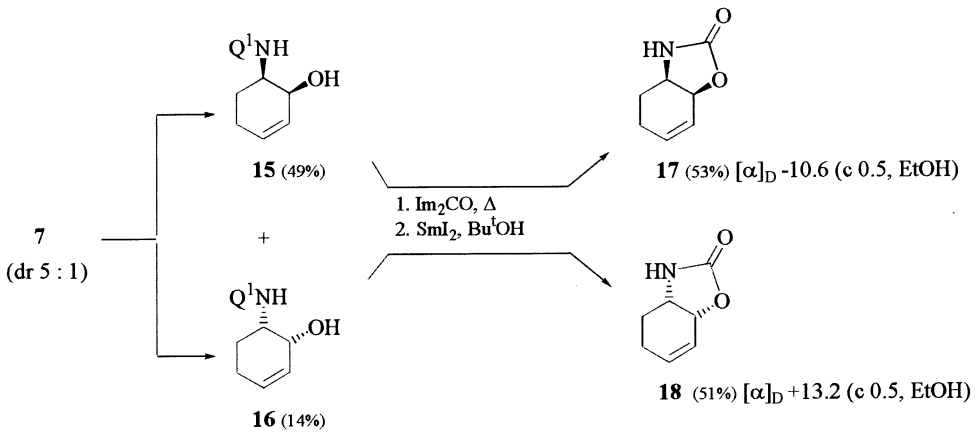


Scheme 4.

Completely stereoselective insertion into C–H bonds is a reaction characteristic of reactive singlet nitrenes and is competitive with aziridination when alkenes are used as substrates.[9] However, products from direct insertion into C–H bonds have not previously been observed using 3-acetoxyaminoquinazolinones or their corresponding nitrenes.[10,11]

When the reaction of Q^2NHOAc **5** with cyclohexa-1,4-diene (Scheme 4) was carried out by first adding triethylamine, conditions known to bring about aziridination of alkenes via the corresponding *N*-nitrene,[9] the yield of the insertion product, dienylamine **14** (4%) was greatly reduced relative to that of the aziridine **13** (60%). It therefore seems unlikely that *N*-nitrenes are the intermediates mediating the formation of these dienylamines in Schemes 3 and 4.

Aziridines **3**, **4** and **7** are potentially useful sources of chirons by ring-opening of the three-membered ring and the removal of the Q^1 group. Thus, aziridine **7** (dr 5:1) was ring-opened by aqueous acetonitrile containing toluene *p*-sulfonic acid with complete retention of configuration[12] to give the diastereoisomeric alcohols **15** and **16** (Scheme 5). Separation of these alcohols and reaction of each with carbonyl diimidazole followed by reduction with samarium diiodide gave the corresponding enantiomeric chirons **17** mp 85–86°C and **18** mp 87–88°C (lit.[13] mp 86–88°C) whose optical rotations were close in magnitude but opposite in sign.



Scheme 5.

Acknowledgements

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References

1. Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.
2. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2783.
3. Q^1NHOAc **1** is prepared from (*S*)-*tert*-leucine.
4. Crystal data for **3a**: $C_{18}H_{21}N_3O_2$, $M=311.18$, monoclinic, space group $P2_1$, $a=8.789(2)$, $b=11.035(3)$, $c=9.229(4)$ Å, $\beta=111.20(4)°$, $U=834.5(5)$ Å^3, $T=190$ K, $Z=2$, μ(Mo Kα)$=0.082$ mm^{-1}, crystal 0.56×0.44×0.16 mm, 1764 reflections measured, 1662 unique ($R_{int}=0.034$). The final $R_1[F^2>2\sigma(F^2)]=0.0415$, ωR_2 (all data)$=0.111$ for 208 parameters. Crystals of **3a** were obtained from diethyl ether.
5. The configuration shown in **4** is assigned by analogy with that of **3a**.
6. Atkinson, R. S.; Barker, E.; Ulukanli, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 583.
7. Occasionally the dr was lower at 4:1 for reasons not as yet clear.
8. A by-product in this reaction was the allyl aryl thioether from S_N2 ring-opening (10%).
9. Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem.* **1968**, *33*, 481; Lwowski, W. In *Nitrenes and Azides, Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984, pp. 205–246.
10. Atkinson, R. S.; Barker, E. *J. Chem. Soc., Chem. Commun.* **1995**, 819.
11. Insertion also occurs into a C*H*H bond of 9,10-dihydroanthracene with Q^1NHOAc **1** in the presence of Ti(OBu^t)$_4$ (12% yield) and into a C*H*H bond of xanthene with Q^2NHOAc **5** (12% yield).
12. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *Tetrahedron Lett.* **1998**, *39*, 4377.
13. Knapp, S.; Kukkola, P. J.; Sharma, S.; Murali Dhar, T. G.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700: the reported NMR spectrum is very similar to those of **17** and **18**.