JKAU: Sci., **vol. 11,** pp. 65-74 (1419 A.H. / 1999 A.D.)

Aziridination of Chalcones with Chiral and Achiral 3-Acetoxyaminoquinazolin-4 (3H)-Ones

HASSAN A. ALBAR
Chemistry Department, King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT. Aziridination of monobenzal- and dibenzalacetone by 3-acetoxyaminoquinazolin-4 (3H)-ones (AAQs) **1x** yielded aziridinyl ketone **2x** and *bis*-aziridinyl ketones **3x**, respectively. The relative configuration of *bis*-aziridinyl ketone **3b** was determined by x-ray crystallography. *Bis*-aziridinyl ketone **5b** was obtained as a single diastereomer from aziridination of *spiro*-2-aziridino -6-benzalcyclohexanone **4a** with AAQ **1k** by what appears to be kinetic resolution.

Introduction

3-Acetoxyaminoquinalin-4 (3H)-ones (AAQs) **1x** are aziridinating agents for alkenes including α,β-unsaturated esters and ketones[1-3]. The presence of a chiral substituent in the 2-position of the quinazolinone ring can give rise to high diastereoselectivity in aziridination of prochiral alkenes (reagent-controlled diastereoselectivity)[4]. On the other hand high diastereoselectivity is also obtained using achiral AAQs and chiral alkenes *e.g.* cyclohex-2-enol[5] and cyclohexe-3-enol[6] (substrate-controlled diastereoselectivity). We have recently reported that *bis*-aziridination of 2,6-dibenzalcyclohexane with AAQs and 1,3-dipolar cycloaddition to *spiro* 2-aziridino-6-benzalcyclohexanone proceed with complete substrate-controlled diastereoselectivity[7].

In this paper we report the results of aziridination of mono- and of dibenzalacetone with chiral and achiral AAQs **1x** and the aziridination of *spiro*-2-aziridino-6-cyclohexanones **4a**-**c** with enantiomerically pure AAQ **1k.**

Experimental

All melting points are uncorrected. Infrared spectra (KBr) were measured on a Perkin-Elmer 298 spectrophotometer or on a Nicolet Magna 520 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in deuteriochloroform on a Varian DPX-400 FT-NMR spectrometer using tetramethylsilane as internal reference. Microanalyses were

performed on a 2400 Perkin Elmer Series 2 CHNS analyser in King Abdulaziz University, Jeddah. Standard MS were recorded on either a Micromass 16B spectrometer or a Kratos 'concept' 1H. Accurate mass measurements were made on the latter at Leicester University. All aziridine derivatives were synthesised by general method as described in the ref. [7]. The prepared aziridines gave accurate mass and the ^{1}H & ^{13}C NMR data for most of the prepared aziridines **2a-f** and **2g-j** recorded in Tables 1 and 2, respectively.

TABLE 1. ^{1}H NMR spectral data of Aziridines **2a-c** and **2d-f.**

	2a	**2b**	**2c**	**2d**	**2e**	**2f**
CH_3CO	2.36	2.38, s	2.38, s	2.55, s	2.55, s	2.53, s
CH_3	2.53	1.37t, J = 7	–	2.47, s	1.25t, J = 7	–
CH_2	–	2.95q, J = 7	–	–	2.82q, J = 7	–
$(\underline{CH}3)_2CH$	–	–	1.37, d, J = 6.6	–	–	1.35, d, J = 6.6
	–	–	1.43, d, J = 6.6	–	–	1.41, d, J = 6.6
$(CH_3)CH$	–	–	3.63, m, J = 6.6	–	–	3.68, m, J = 6.6
$\underline{CH_x}$-CH	2.85dd, J = 1,5	2.82*	2.88, dd, J = 1,5	3.94d, J = 4.4	3.93d, J = 4.4	3.93d, J = 4.4
	3.12dd, J = 1,8	3.04*	3.18, dd, J = 1,8			
CH_x-$\underline{CH}$	3.74dd, J = 5,8	3.53dd, J = 5,8	3.74, dd, J = 5,8	3.96d, J = 4.4	3.95d, J = 4.4	3.97d, J = 4.4
8-H	7.41 m	7.43 m	7.43, m	7.41+ m	7.42+ m	7.41+ m
6-H, 7-H	7.70 m	7.74, m	7.70, m	7.70, m	7.70, m	7.70, m
5-H	8.16d, J = 6	8.18d, J = 6	8.16, d, J = 6	8.14, d, J = 6	8.14, d, J = 6	8.14, d, J = 6
C_6H_5	–	–	–	7.41+ m	7.42+ m	7.41+ m

* : Overlaps signals; x = 2 for aziridines 2a-c and x = 1 for aziridines 2d-f; J (Hz); + : Overlap signals

TABLE 2. ^{1}H NMR spectral data of Arizidines **2g-j.**

	2g	**2h**	**2i**	**2j**
CH^3	2.59	1.16t, J = 7	–	1.06$, s
CH^2	–	2.79q, J = 7	–	2.45d+, J = 14
				2.28d+, J = 14
$(\underline{CH_3})^2$ CH	–	–	1.21, d, J = 6.6	–
	–	–	1.43, d, J = 6.6	–
$(CH_3)C\underline{H}$	–	–	3.36, m, J = 6.6	–
$\underline{CH}$-CH	4.18d, J = 4.4	4.20d, J = 4.4	4.18, d, J = 4.4	3.94d, J = 4.4
CH - $C\underline{H}$	4.24d, J = 4.4	4.27d, J = 4.4	4.28, d, J = 4.4	3.96d, J = 4.4
5 - H	8.14d, J = 6	8.10d, J = 6	8.11d, J = 6	8.14, d, J = 6
$2C_6H_5^{\#}$	7.03-7.75m	7.01-7.76m	7.01-7.82m	7.01-7.76m

* : Overlap signals; J (Hz); # : Overlap with the 6-H & 7-H & 8-H of the quinazolinone ring and – CO-C$\underline{H}$ = C$\underline{H}$-; $: Three methyl groups (9H); + : Diasterotopic protons.

5b: ^{1}H NMR ($CDCL_3$) δ : 1.40 (3h, d, J = 6 6.6 Hz, [CH(OH)Me]), 2.20 (6H, m, $(CH_2)_3$), 2.48 (3H, s, Me), 4.17 & 4.08 (2 × 1H, s, 2x aziridine ring proton), 4.53 (1H, d, J = 6Hz, [CH(OH)Me], 4.92 (1H, quintet, J = 6Hz, [CH(OH)Me], 7.53 (16H, m, Ar-H) and 8.10 and 8.15 (2 × 1H, 2d, J = 8 Hz, 2 × 5-H in the quinazolinone ring); ^{13}C NMR ($CDCl_3$) δ : 22.8 and 23.2 ($2CH_3$), 18.4 and 27.8 ($3CH_2$), 56.9 and 57.2 (2 spiro carbon, do not appeared in the DEPT technique), 62.6 and 64.2 (2CH), 159.2 and 159.3 (2CON) and 188.0 (CO).

X-ray Crystallography Data for 3h

$C_{37}H_{34}N_3O_3$, M = 610.7, monoclinic, space group C2/C, a = 17.542(4), b = 16,165 (4), c = 12.412(3) Å, β = 120.54(2)º, V = 3031.4(13) Å^3 (By least squares refinement on diffractometre angles for 32 centred reflections in the rang 2.52 < θ < 24.00º), z = 4, D∈ = 1.338 Mg/m^3, μ (Mo - Kα) = 0.087 mm^{-1} colourless block (from ethanol), crystal dimensions 0.53 × 0.26 × 0.18 mm.

Data collection and processing: Data were measured on Siemens P4 diffractometre at 190 K using graphite monochromated Mo-Kα radiation [λ = 0.71073 Å] using an ω scan technique. Three standard reflection monitored every 100 scans showed no significant variation in intensity, the reflections were corrected for Lorentz and polarisation effects 2860 data were measured (2.52 < θ < 24.00º), with 2388 independent reflections (merging R_{int} = 0.0274) and 2388 having [I > 2σ (I) regarded as observed.

Structure solution and refinement: The structures were solved by direct methods using the program SHELXTL-PC[8] and refined by full-matrix least-squares on F^2 using the program SHELXL93[9]. All hydrogen atoms were included in calculated positions (C-H = 0.96 Å) using a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters. Full-matrix least-squares based on F^2 gave R1 = 0.0850, ωR2 = 0.1153 for all data, for 209 parametres (R factors defined in Ref. 7), weighing scheme ω = 1 / [$\sigma^2(F_0^2) + (0.096P)^2 + 1.63P$] where P = [max. (F_0^2 , 0) + $2F_c^2$] / 3, GOF = 1.039. The maximum and minimum electron densities in the final ΔF map were 0.200 and –0.485 eÅ^{-3}.

X-ray Crystallography data for 4a$_1$ and 4a$_2$

$C_{30}H_{27}N_3O_3$, M = 477.55, monoclinic, space group P1, a = 9.896(1), b = 10,811(2), c = 12.524(2) Å, α = 111.38(3)º, β = 104.23(2)º, γ = 90.90(1)º, V = 1201.1(5) Å^3 (By least squares refinement on diffractometre angles for 32 centred reflections in the rang 2.78 < θ < 23.50º), z = 5, Dε = 1.320 Mg/m^3, μ (Mo – Kα) = 0.086 mm^{-1} colourless block (from ethanol), crystal dimensions 0.44 × 0.14 × 0.13 mm.

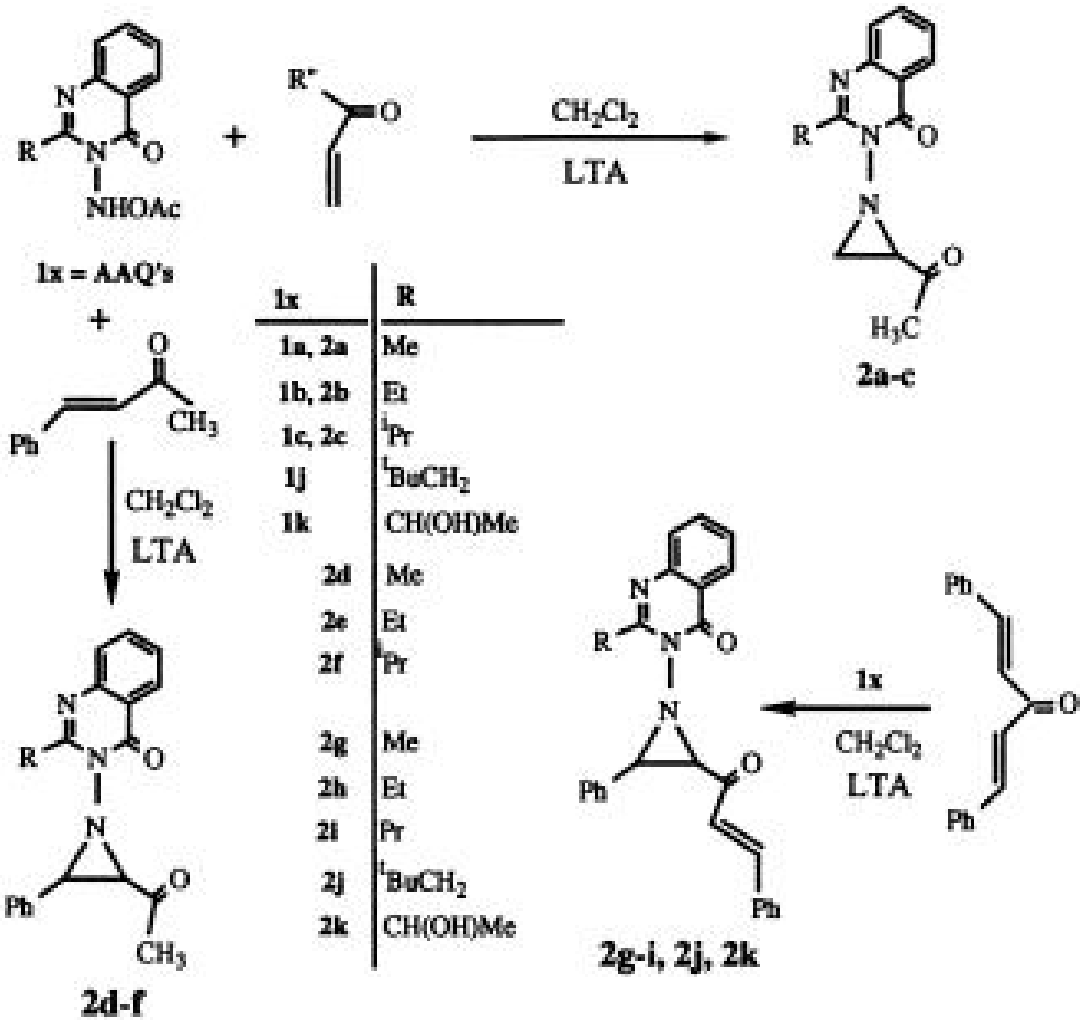
Data collection and processing: Data were collected and processed as for **3h.** 3878 data were measured (2.78 < θ < 23.50º), with 3876 independent reflections (merging R_{int} = 0.0000) and 3876 having [I > 2σ(I)] regarded as observed .

Structure solution and refinement: The structures were solved using same method as **3h.** Full-matrix least-squares based on F^2 gave R1 = 0.0790, ωR2 = 0.1729 for all

data, for 328 parameters (R factors defined in Ref. [7]), weighing scheme $\omega = 1 / [\sigma^2 (F_0^2) + (0.065P)^2 + 1.39P]$ where $P = [\max. F_0^2, 0) + 2F_c^2] / 3$, GOF = 1.016. The maximum and minimum electron densities in the final ΔF map were 0.337 and –0.336 eÅ^{-3}.

Result and Discussion

Reactions of AAQs (**1a**-**c**) prepared in dichloromethane solution by lead tetra-acetate oxidation of the corresponding 3-aminoquinazolinones at –20ºC, with methyl vinyl ketone and with benzalacetone gave the corresponding aziridines **2a**-**c** and **2d**-**f**, respectively, in good yields (Scheme 1). The ^{1}H NMR (400MHz, $CDCl_3$) data of aziridine derivatives **2a**-**c** summarized in Table 1.

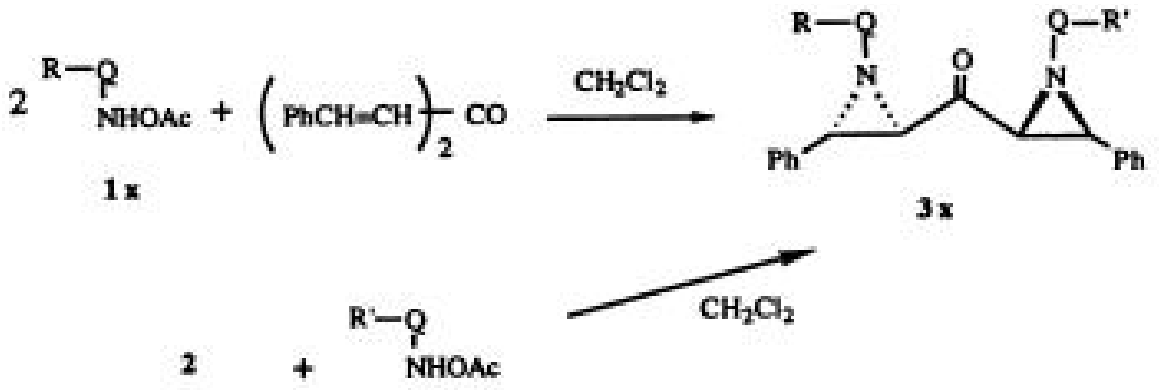


Scheme 1

Similarly, the reaction of **1a**-**c** and **1k** with dibenzalacetone afforded aziridines **2g**-**1** and **2j** respectively, in good yield. For example, for aziridine **2g :** MS (FAB) $M^+ + 1$, 408; for aziridine **2i :** MS (FAB) $M^+ + 1$, 436; Acc. Mass Found M^+ 436.2025, $C_{28}H_{26}N_3O_2$, Calc. M^+ 436.2025. The ^{1}H NMR data for aziridine derivatives **2g**-**i** and **2j** summarized in Table 2.

The enantiomerically pure **1k** reacts with dibenzalacetone to afford a pair of diastereosomers $\mathbf{2_1k}$ and $\mathbf{2_2k}$ in 6:4 ratio: when this aziridination was repeated in the presence of Ti(IV)-tert-butoxide[4], the ratio of these diastereoisomers was changed to 9:1 (yield 35%) (Scheme 1).

Further aziridination of the remaining double bond in aziridines **2g-j** byAAQs **1a-c** and **1j** afforded the corresponding diaziridinyl ketones **3g-j.** The latter aziridines were also synthesised by aziridination of dibenzalacetone (1 mol equiv.) with AAQ **1a-c, j** (2 mol. equiv.) as shown in Scheme 2. For example, aziridine **3h :** MS (FAB) $M^+ + 1$, 608; Acc. Mass Found M^+ 609.2614, $C_{37}H_{33}N_6O_3$, Calc. M^+ 609.2614; ^{1}H NMR (400MHz, $CDCl_3$) : δ 1.22 (3H,t, J = 7.3Hz, $CH_2C\underline{H}_3$), 2.79 (2H, q, J = 7.3Hz, $C\underline{H}_2CH_3$), 3.83 (1H, d, J = 4.4Hz, CH), 4.52 (1H, d, J = 4.4Hz, CH), 7.51 (16H, m, Ar-H) and 7.98 (2 × 1H, d, J = 6.6Hz, 2 × 5-H of the quinazolinone ring); ^{13}C NMR (400MHz, CDC_{13}) : δ 10.5 and 10.7 ($2\underline{C}H_3$), 27.7 and 27.8 ($2\underline{C}H_2$), 54.5 and 56.7 (2CH), 155.8 and 159.2 (2CON-) and 184.4 (CO). Aziridine **3j :** MS (FAB) $M^+ = 1$, 693; Acc. Mass Found M^+ 693.3553, $C_{43}H_{45}N_6O_3$, Cald. M^+ 693.3554. The structure and relative configuration of the diaziridinyl ketone **3h** was confirmed by x-ray crystallography (Fig. 1).



1x : R = 1a :Me, 1b :Et, 1c :^{i}Pr, 1j :^{t}BuCH$_2$, 1k :CH(OH)Me

3x : R, R' = 3g :Me; 3h :Et; 3i :^{i}Pr; 3j :^{t}BuCH$_2$; 3k :CH(OH)Me; 3hk :Et, CH(OH)Me.

Scheme 2

It is clear, therefore, that the first aziridination ring introduced has a directing effect on which diastereoface of the residual α,β-unsaturated ketone is aziridinated ketone is aziridinated by the AAQ. The sense of diastereoselectivity is in agreement with attack on the conformation shown in Fig. 2 and supports the *trans*-configuration assigned to the *spiro*-2,6-*bis* aziridinocyclohexanone **x** prepared previously[7].

Reaction of the double bond in racemic aziridine **2h** with enantiomerically pure **1k** gave *bis*-aziridinoketone apparently as a single diastereoisomer **3hk.** The unreacted azirdinyl ketone **2h** in this aziridination should be enriched in one enantiomeric form *i.e.* kinetic resolution could have occurred and this point is under investigation.

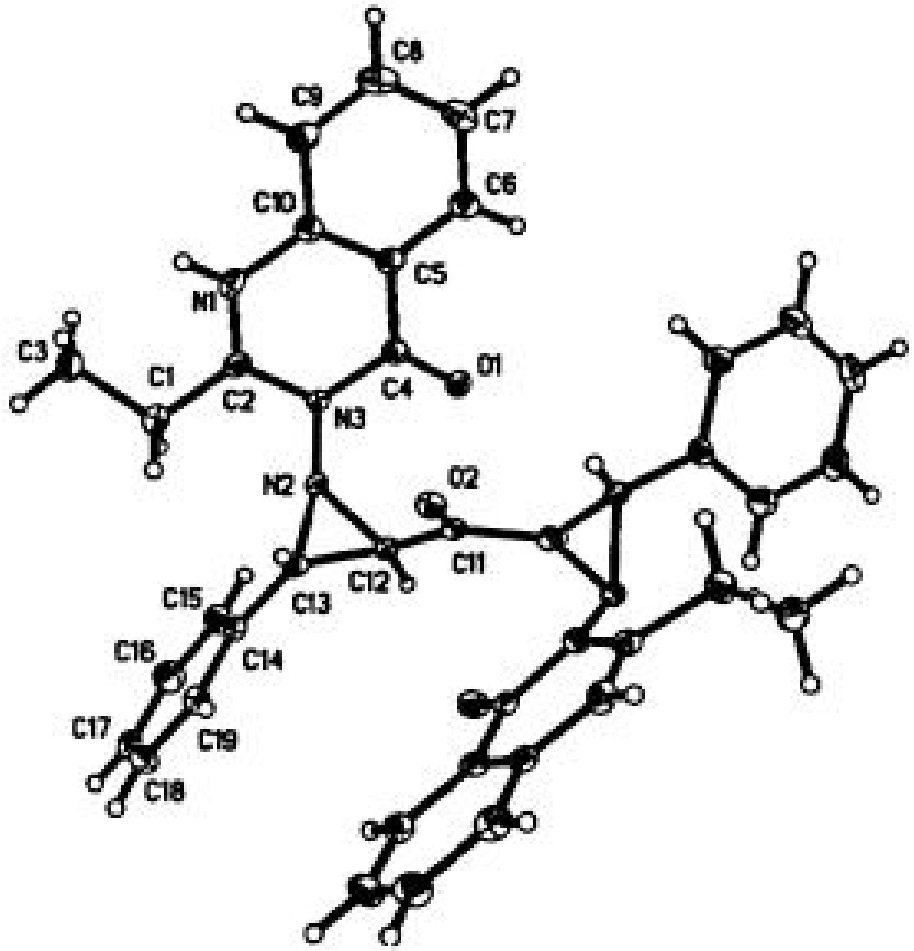


FIG. 1. X-ray crystal structure of aziridine **3h.**

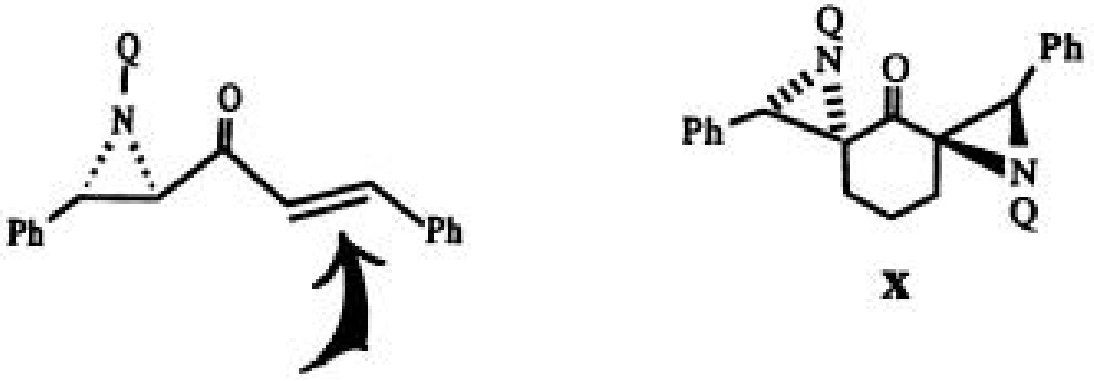
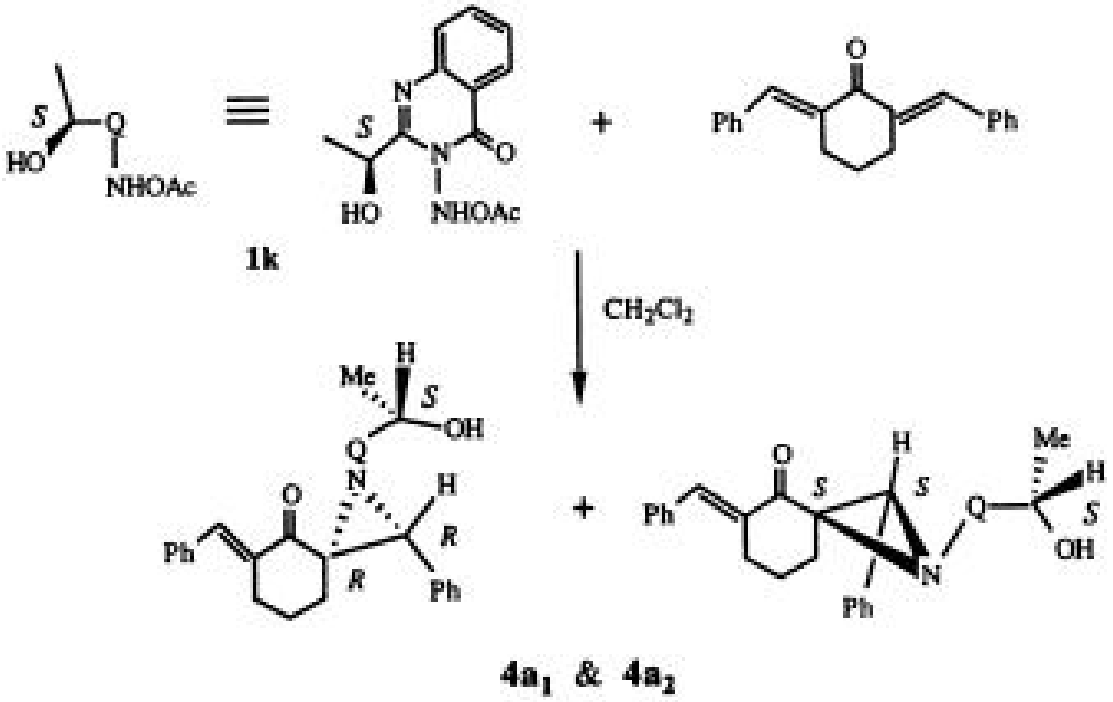


FIG. 2.



Scheme 3

Aziridination of 2,6-dibenzalcyclohexanone with **1k** gave two enantiopure diastereoisomers $\mathbf{4a_1}$ and $\mathbf{4a_2}$ in a 6:4 ratio in moderate yield, [mp 173-174ºC, yield 58% Acc. Mass Found : M^+ 477.2053, $C_{30}H_{27}N_3O_3$, Calc. M^+ 477.2053] (Scheme 3). The ^{1}H NMR (400MHz) spectrum of $\mathbf{4a_1}$ showed a doublet for the [CH(OH)Me] at δ 1.33, a singlet for the aziridine ring proton at δ 4.47, a doublet for CH(OH)Me at δ 4.64 and a quintet for CH(OH)Me at δ 4.95. In $\mathbf{4a_2}$, the corresponding signals were at δ 1.57 [CH (OH)Me], δ 4.47 (aziridine ring H) and δ 4.75 [CH(OH)Me, (broad signal)]. The major diastereoisomer, $\mathbf{4a_1}$ was isolated (~ 90% pure), (Scheme 3): X-ray crystallography on a single crystal from this mixture shows the presence of both *SSS* and *SRR* enantiopure diastereomers, $\mathbf{4a_1}$ and $\mathbf{4a_2}$ as shown in Fig. 3.

Aziridination of *spiro* 2-aziridino-6-benzalcyclohexanones **4a** and **4b** with the enantiomerically pure 3-acetoxyaminoquinazoline **1k** yield **5a** and **5b** respectively (Scheme 4) which appear to be single diastereoisomers : **5b** has $[\alpha]_{20}^{CHCl_3} = 96^o$ at λ = 589 nm, $[\alpha]_{20}^{CHCl_3} = 100^o$ at λ = 578 nm, $[\alpha]_{20}^{CHCl_3} = 121.5^o$ at λ = 546 nm, $[\alpha]_{20}^{CHCl_3} = 311^o$ at λ = 436 nm, $[\alpha]_{20}^{CHCl_3} = 1286.5^o$ at λ = 365 nm.

Reduction of 2-aziridino-6-benzalcyclohexanone **4c**[7] by sodium borohydrite in an ethanol-water mixture for 3 hours at room temperature gave the corresponding cyclohexanol **6c** in good yield, [MS (FAB) : [M^+ = 1] = 464 (35%); (EI) : m/z(%), 463 (M^+, 65)] as shown in Scheme 4. As in the bis-aziridine above, attack of hydride appears to be from one face of the carbonyl group since alcohol, **6c** is a diastereoisomer. The X-ray crystal structures of **4c**[7] strongly suggests that attack of hydride on the carbonyl group will be opposed to the aziridine ring and that the relative configuration of alcohol **6c** should be as shown above.

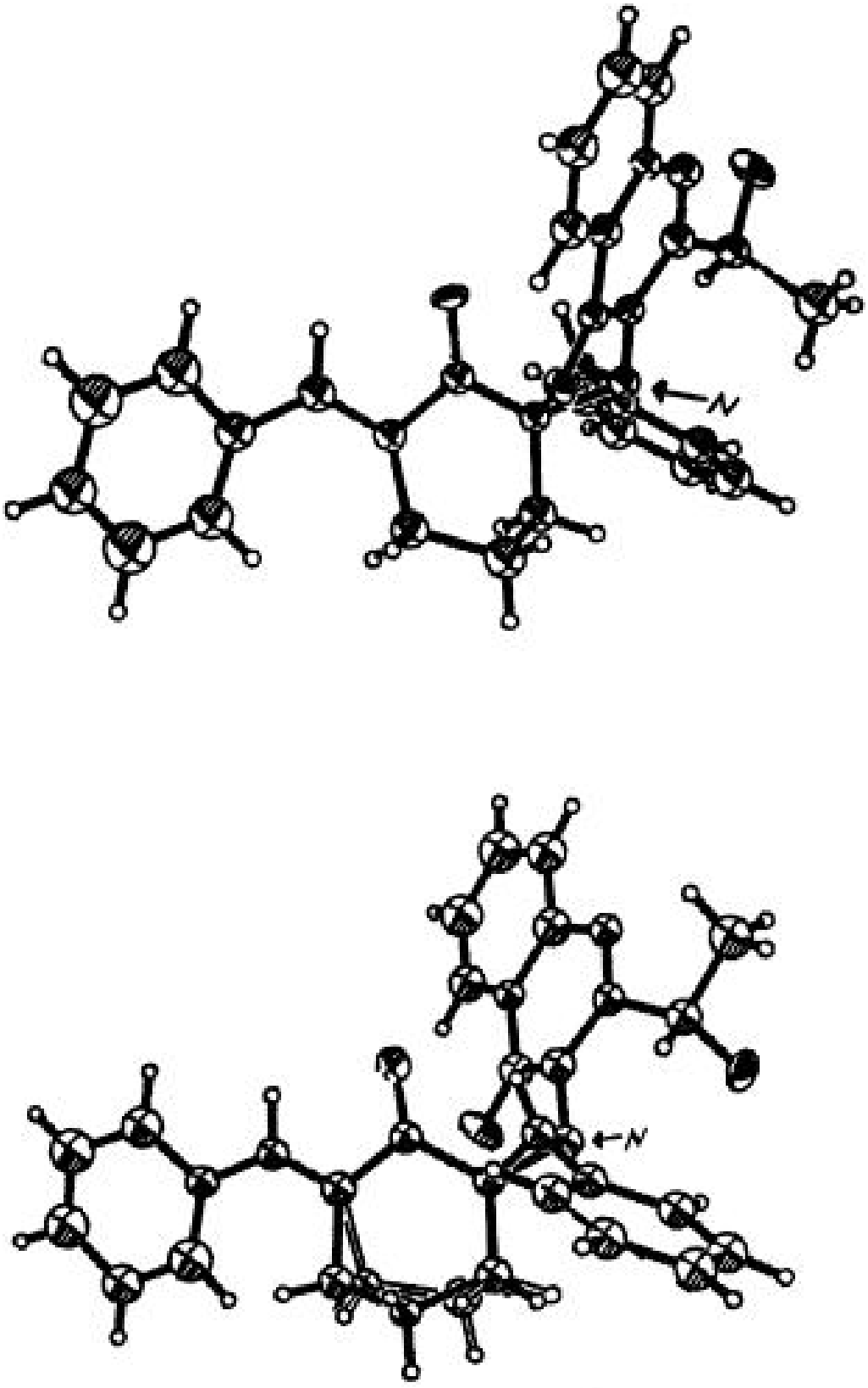
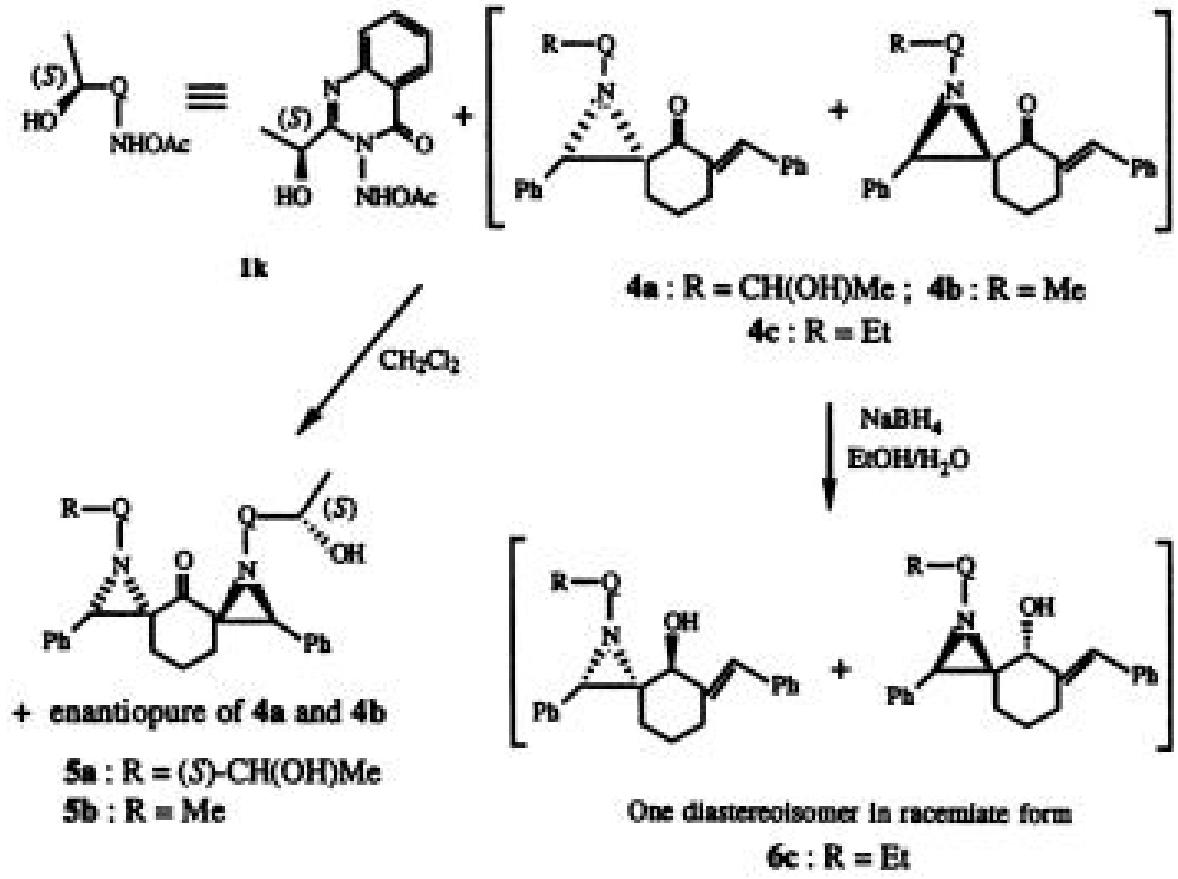


FIG. 3. X-ray crystal structure of mixture of enantiopure diastereomers **4a$_1$** and **4a$_2$.**



Scheme 4

Acknowledgements: I would like to thank Dr. Robert S. Atkinson for his help in this work and Drs J. Fawcett and D.R. Russell for the X-ray data, and the University of Leicester (UK) and KACST (Saudi Arabia) for support.

References

[1] **Atkison, R.S., Barker, E.** and **Ulukanli, S.,** *J. Chem. Soc., Perkin Trans.* **1:** 583 (1998); **Atkinson, R.S., Barker, E., Meades, C.K.** and **Albar, H.A.,** *Chem. Commun.* **29** (1998).

[2] **Atkinson, R.S.** and **Barker, E.,** *J. Chem. Soc., Chem. Commun.,* **819** (1995); **Atkinson, R.S., Coogan, M.P.** and **Cornell, C.L.,** *J. Chem. Soc., Perkin Trans.* **1:** 157 (1996).

[3] **Atkinson, R.S., Fawcett, J., Russell, D.R.** and **Williams, P.J.,** *Tetrahedron Letters,* **36:** 3241 (1995); **Atkinson, R.S., Barker, E., Edwards, P.J.** and **Thomson, G.A.,** *J. Chem. Soc., Perkin Trans.* **1:** 1533 (1955).

[4] **Atkinson, R.S., Gattrell, W.T., Aycough, A.P.** and **Raynham, T.M.,** *Chem. Commun.,* 1935 (1995).

[5] **Atkinson, R.S., Kelly, B.J.,** *J. Chem. Soc. Perkin Trans.* **1:** 1515 (1989).

[6] **Atkinson, R.S., Kelly, B.T.** and **McNicholas, C.,** *Chem. Commun.* 562 (1989).

[7] **Albar, H.A., Fawcett, J.** and **Russell, D.R.,** *Heterocycles,* **45:** 1289 (1977).

[8] **Shelddrick, G.M.,** *SHELXTL-PC, Release 4.2, Siemens Analytical X-Ray Instruments, Madison, WI,* (1991).

[9] **Sheldrick, G.M.,** *SHELX-93, Program for Crystal Structure Refinement,* University of Gottingen (1993).

أزيردة الشالكونات باستخدام مركبات الكيرالية وغير الكيرالية من 3-أسيتوكسي أمينوكوينازولين-(3H)4-أون

حسن بن عبد القادر بن حسن البار
قسم الكيمياء ، كلية العلوم ، جامعة الملك عبد العزيز
جـــدة - المملكة العربية السعودية

المستخلص . أزيردة بينزال - والداي بينزال أسيتون باستخدام 3-أسيتوكسي أمينوكوينازولين-(3H)4-أون 1x تعطي أزيريدينايل كيتون 2x وثنائي أزيريدينايل كيتون 3x على التوالي . وقد أوضحت نتيجة تحليل الأشعة السينية التشكيل الفراغي وهيئة الكيتون 3x . كما تم تشييد ثنائي الأزيريدينايل كيتون 5b في صورة تمارئية نقية على هيئة دایاستيريومر منفرد من تفاعل الإسبيرو 2-أزيريدينو-6-بينزال سايكلوهكسانون 4a مع 3-أسيتوكسي أمينوكوينازولين-(3H)4-أون 1k لربما بمسار الفصل الحركي .