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

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Abstract. Aziridination of monobenzal- and dibenzalacetone by 3-aceto-xyaminoquinazolin-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

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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$_3$CO	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	–
(CH3)$_2$CH	–	–	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
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$_x$-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$_6$H$_5$	–	–	–	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$, s
CH^2	–	2.79q, J = 7	–	2.45d+, J = 14
				2.28d+, J = 14
(CH$_3$)^2 CH	–	–	1.21, d, J = 6.6	–
	–	–	1.43, d, J = 6.6	–
(CH$_3$)CH	–	–	3.36, m, J = 6.6	–
CH-CH	4.18d, J = 4.4	4.20d, J = 4.4	4.18, d, J = 4.4	3.94d, J = 4.4
CH - CH	4.24d, J = 4.4	4.27d, J = 4.4	4.28, d, J = 4.4	3.96d, J = 4.4
5 - H	8.14d, J = 6	8.10d, J = 6	8.11d, J = 6	8.14, d, J = 6
2C$_6$H$_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-CH = CH-; $
: Three methyl groups (9H); + : Diaserotopic protons.

5b: ^{1}H NMR (CDCL$_3$) δ : 1.40 (3h, d, J = 6 6.6 Hz, [CH(OH)<u>Me</u>]), 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(O<u>H</u>)Me], 4.92 (1H, quintet, J = 6Hz, [C<u>H</u>(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$_3$O$_3$, 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 / [σ^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$_3$O$_3$, 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, D∈ = 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.
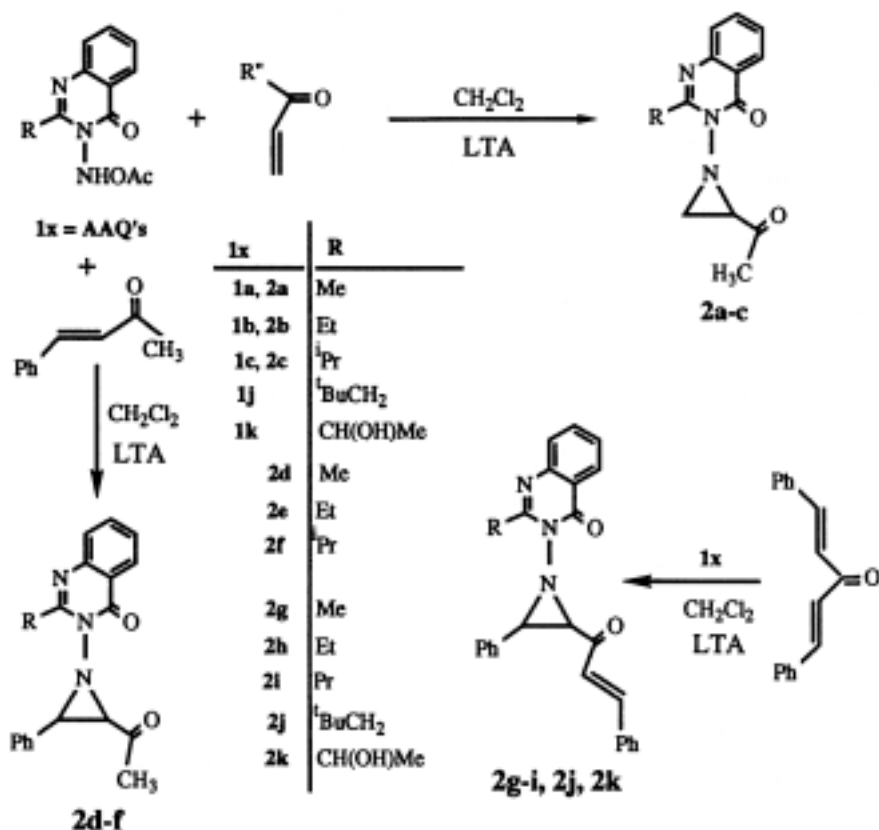
Scheme 1

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 **2₁k** and **2₂k** 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$_6$O$_3$, Calc. M$^+$ 609.2614; ^{1}H NMR (400MHz, CDCl$_3$) : δ 1.22 (3H,t, J = 7.3Hz, CH$_2$CH$_3$), 2.79 (2H, q, J = 7.3Hz, CH$_2$CH$_3$), 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$_{l3}$) : δ 10.5 and 10.7 (2CH$_3$), 27.7 and 27.8 (2CH$_2$), 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$_6$O$_3$, 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.
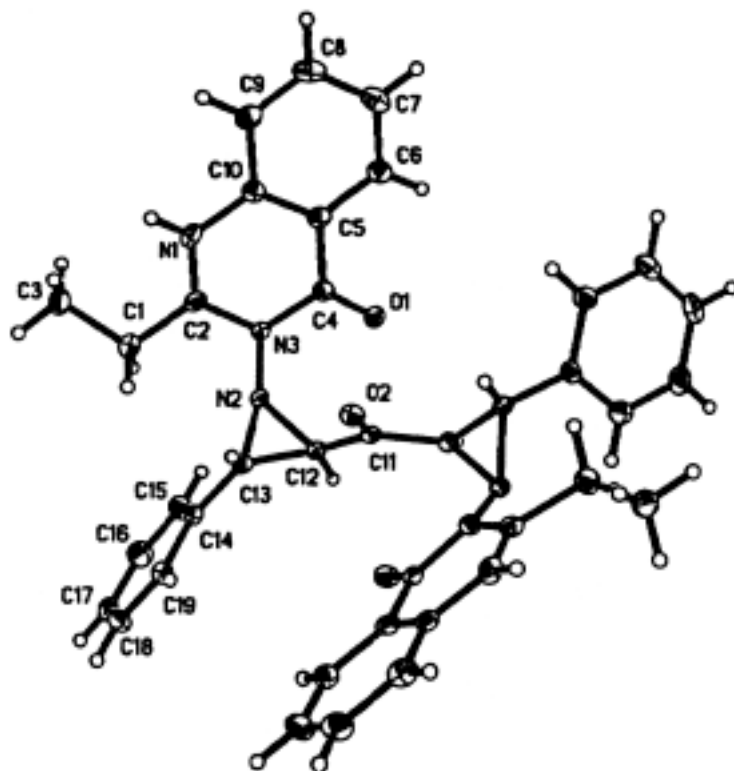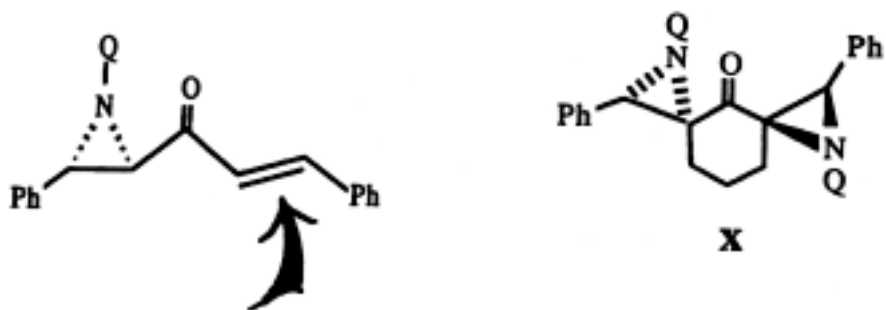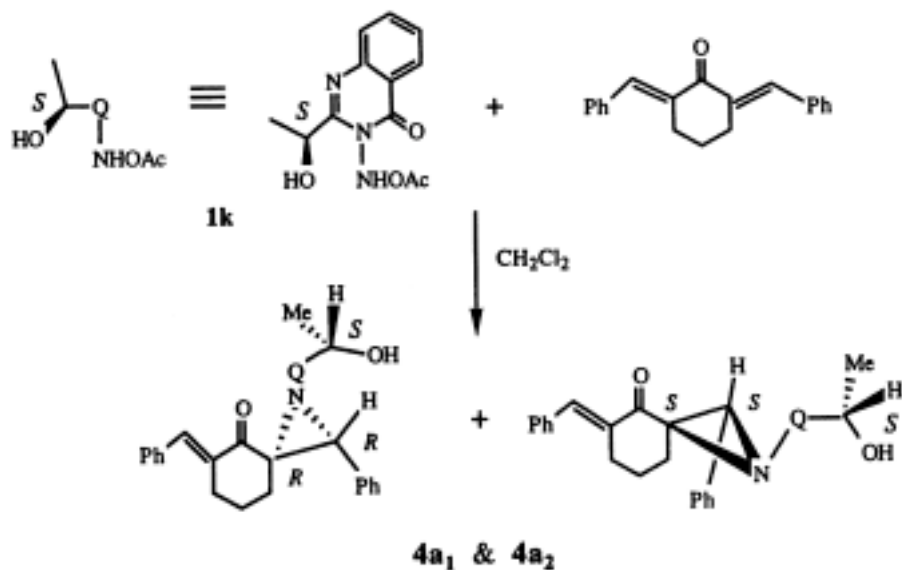
FIG. 1. X-ray crystal structure of aziridine **3h.**

FIG. 2.

Scheme 3

Aziridination of 2,6-dibenzalcyclohexanone with **1k** gave two enantiopure diastereoisomers **4a₁** and **4a₂** in a 6:4 ratio in moderate yield, [mp 173-174°C, yield 58% Acc. Mass Found : M⁺ 477.2053, $C_{30}H_{27}N_3O_3$, Calc. M⁺ 477.2053] (Scheme 3). The ¹H NMR (400MHz) spectrum of **4a₁** 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 **4a₂**, 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, **4a₁** 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, **4a₁** and **4a₂** 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 $[\alpha]_{20}^{CHCl_3} = 96°$ at λ = 589 nm, $[\alpha]_{20}^{CHCl_3} = 100°$ at λ = 578 nm, $[\alpha]_{20}^{CHCl_3} = 121.5°$ at λ = 546 nm, $[\alpha]_{20}^{CHCl_3} = 311°$ at λ = 436 nm, $[\alpha]_{20}^{CHCl_3} = 1286.5°$ 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.
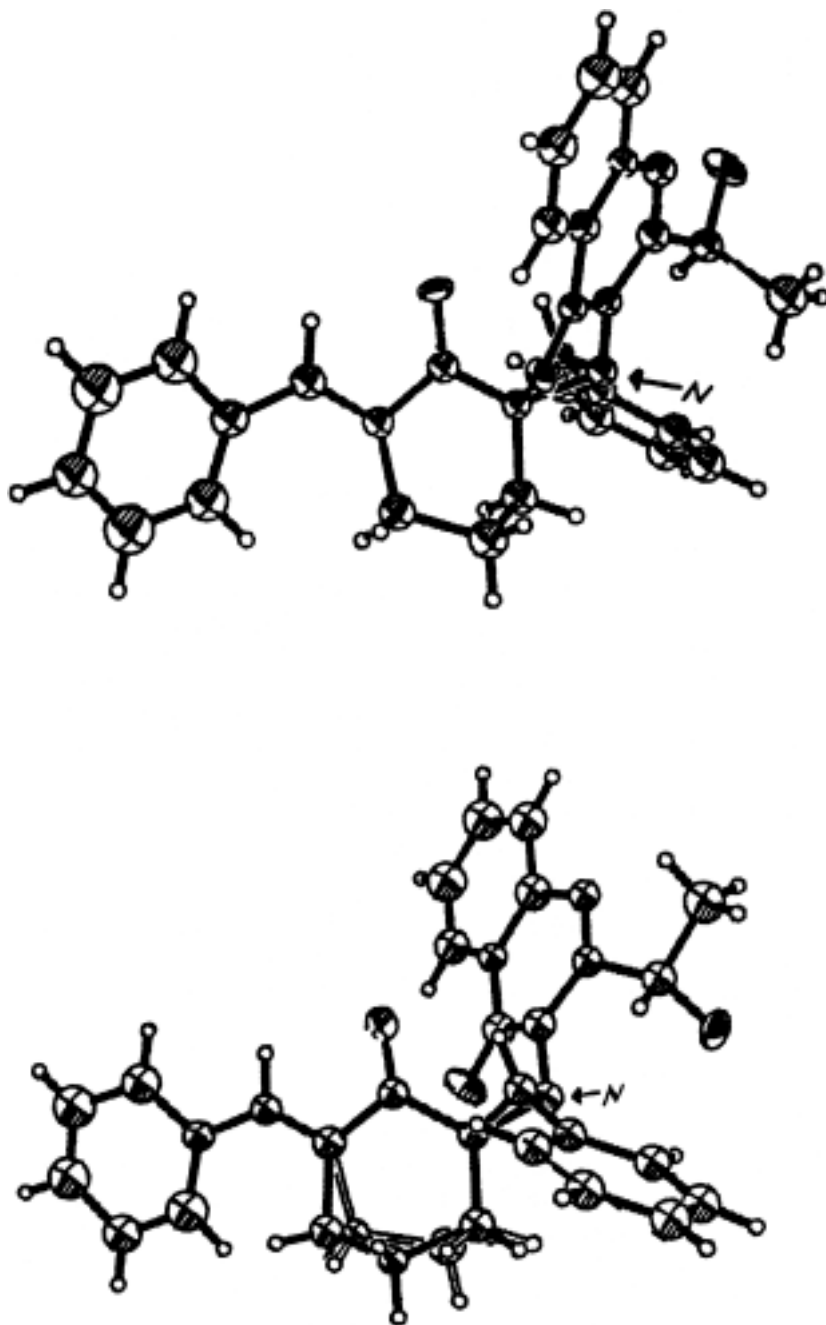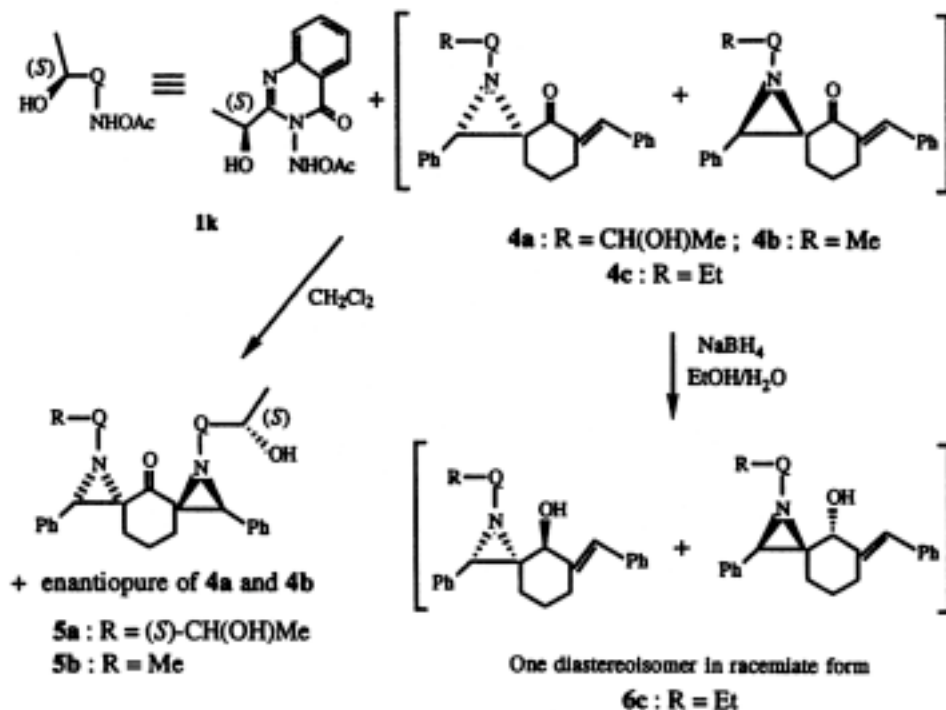
F<small>IG</small>. 3. X-ray crystal structure of mixture of enantiopure diastereomers **4a₁** and **4a₂.**

Scheme 4

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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

جـــــدة – المملكة العربية السعودية

المستخلص .   أزيردة بينزال – والداي بينزال أسيتون باستخدام 3–أسيتوكسي أمــينوكــوينازولين–(3H)4–أون 1x تعطي أزيريدينايل كـيــتــون 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 داياستيريومر منفرد من تفاعل الإسبيرو 2– أزيريدينو–6–بينزال سايكلوهكسانون 4a مع 3–أسيتوكسي أمينوكوينازولين–(3H)4–أون 1k لربما بمسار الفصل الحركي .