Synthesis of Oxazole and 4-Oxazolone Derivatives via α -aminonitriles

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Abstract

The scheme of this work included preparation of oxazole and 4-oxazolone derivatives starting from α-aminonitriles which were prepared according to the modified Strecker's method. Treatment of α-aminonitriles with 90% sulfuric acid on a steam bath for 10 minutes produced α-aminoamides which produced oxazole derivatives upon treatment with p-bromophenacyl bromide, and 4-oxazolone derivatives upon treatment with chloro acetic acid.

Introduction

Oxazole and 4-oxazolone derivatives were chosen as a target for this work because many of their derivatives are known to possess antibacterial, antimicrobial, antiviral, analgesic[1-3] and pharmacological activities such as Indolmycine[4]. Diels-Alder reaction of oxazoles was used as synthetic root to vitamin B1 analogues[5].

Oxazoles are obtained by the reaction of α-aminoamides with α-haloketones according to Hantzsch's method[10]. Refluxing α-aminoamides with α-chloroacetic acid in absolute ethanol produced 4-oxazolone derivitiaves. The α-aminoamides were prepared by the hydrolysis of α-aminonitriles which were prepared according to the modified Strecker's method[11].

Experimental

Melting points were determined using a Gallen Kamp melting point apparatus and are uncorrected. IR spectra (KBr disc) were recorded on a Pye-Unicam Sp3-300. ^{1}H NMR spectra were recorded using Brucker 250 MHz with tetramethylsilane as internal standard in deuterated chloroform or DMSO. Measurements were made at the Chemistry Department, Mu'ta University, Jordan. Thin layer chromatography was carried out using Fertigfolien pre-coated silica sheets and the plates were developed with iodine vapor.

General procedure for preparation of compounds

α-Aminonitriles:

α-Aminonitriles were prepared using a modified Strecker's procedure. Cyclohexanone (0.05) mol was dissolved in glacial acetic acid 50 mL followed by the addition of 0.05 mol of a primary amine (m-toluidine, o-toluidine, o-anisidine, 4-chloro o-anisidine, o-bromo aniline, o fluoro aniline and p-nitro aniline). The pH was then adjusted to 3-4 with concentrated H_2SO_4 followed by the adition of potassium cyanide 0.05 mol. The reaction mixture was kept stirring overnight, poured on ice and made slightly alkaline with ammonia. The solid which was formed was filtered, washed with water and dried. Purity of the obtained compounds was checked by TLC using chloroform and ethyl acetate (75, 25) as eluent. Recrystallization from ethanol and water (1:1), gave the pure products.

Table 1 lists m.p. and percent yield of the prepared α-aminonitriles. Figure 1 shows the ^{1}H NMR spectrum as an example of compound (5) of the prepared nitrile compounds.

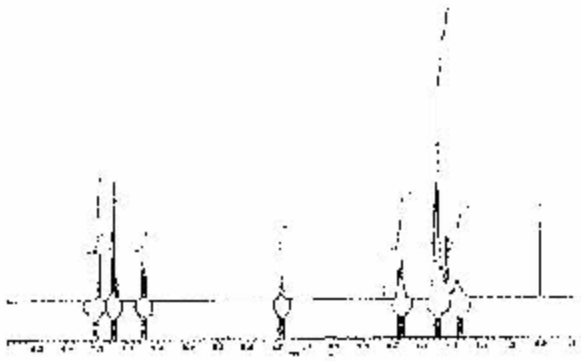

Figure (1): H NMR xpectrum for N-(2-Bromo phenyl)-1-cyano cyclohexyte-amine (5).

α-Aminoamides:

α-Aminoamides were prepared by treatment of α-aminonitriles 1gm with 10ml 90% sulfuric acid on a steam bath for 10 minutes. The mixture was then cooled to room temperature and poured onto crushed ice and made alkaline with ammonia. The solid was filtered, washed with water and dried. Ethanol water mixture was used for recrystallization.

Table 2 lists m.p. and percent yield of the prepared α aminoamides. Figure 2 shows the ^{1}H NMR spectrum as an example of compound (14) of the prepared amide compounds.

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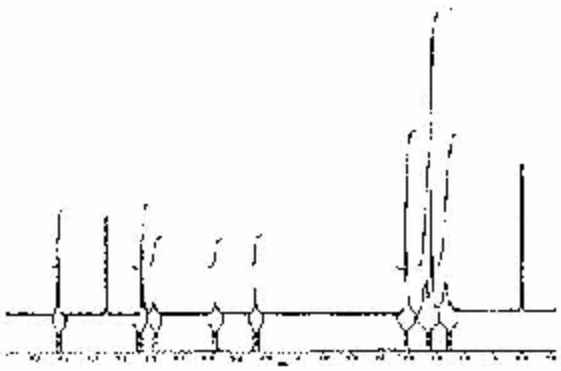

Figure (2): H NMR spectrum for N-(4-Nitro phenyl)-L-carbamoyl-cyclohexyle amine (14).

Oxazoles:

To alcoholic solution of p-bromo phenacyl bromide an equimolecular amount of the α-aminoamide was added and the mixture was kept under reflux for about 6-8 hours. The disappearance of the amide spot and appearance of a higher spot on TLC indicated the formation of the oxazole. The excess solvent was removed by evaporation and the remaining mixture was poured on crushed ice and stirred to obtain the expected oxazole as solid which was filtered, washed with water and dried. Ethanol was used for recrystallization.

Table 3 lists m.p. and percent yield of the prepared oxazoles. Figure 3 shows an example of ^{1}H NMR spectrum of the prepared oxazole (16).

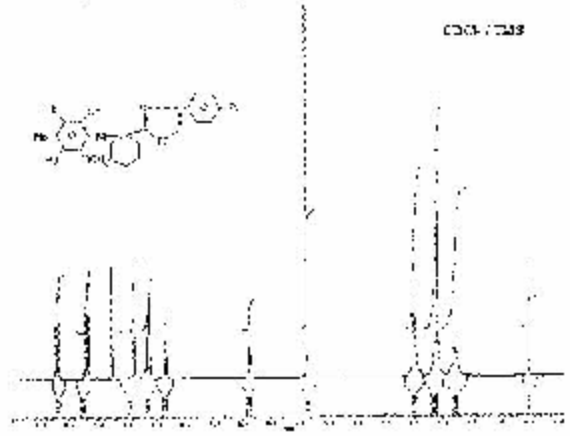

Figure (3): H NMR spectrum for 1-[4-(p-Bromo phenyl)-oxazol-2-yl]-N-(2-Methoxy phenyl)-cyclohexyle amine (16).

4-Oxazoline, 4-hydroxy oxazole:

A mixture of equimolecular amounts of α-aminoamides and chloroacetic acid were refluxed for 24 hours using absolute ethanol as a solvent. Excess ethanol was evaporated and the mixture was poured on crushed ice. The formed solid was filtered and recrystallized using ethanol and water (1:1). The end of the reaction was checked by TLC.

Table 4 lists m.p. and percent yield of the prepared oxazolones. Figure 4 shows the ^{1}H NMR spectrum as an example of compound (19) of the prepared oxazolone compounds.

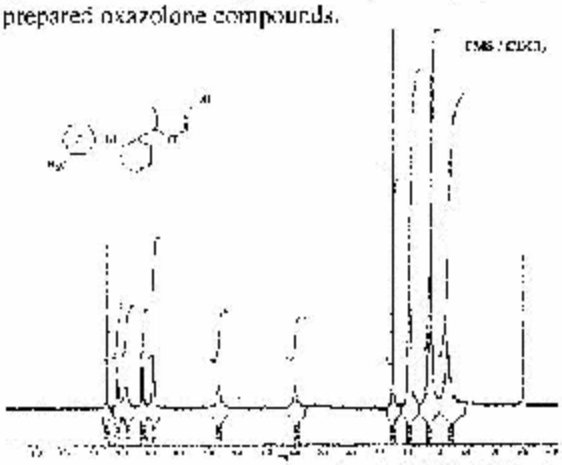

Figure (4): H NMR spectrum for 2-[N-(3- Methyl phenyl)-cyclohexyle amine] 4-hydroxy oxazole(19).

Results and Discussion

The importance of preparing new α-amino nitriles arises from their versatility as starting material for the synthesis of many functionalized organic compounds such as α-amino amides, α-amino acids, thiazoles, thiazolones[12], oxazoles and oxazolones [13]. To achieve this, different primary amines were reacted with cyclohexanone.

The preparation of the α-amino nitriles was achieved by a method depended on the formation of imine, which was first discovered by Schiff[14].

The pH of the reaction mixture was maintained at 3-4 using glacial acetic acid and by adding concentrated sulfuric acid dropwise, so the formed imine could be transformed to an iminium ion and then to accept the CN ion giving the desired α-amino nitriles.

The IR spectra of the prepared α-amino nitriles (1-7) showed the main characteristic bands at ν_{max} 3380-3320 cm^{-1} for NH stretching vibration and at ν_{max} 2200-2210 cm^{-1} for C≡N, in addition to the bands which had been assigned to the aromatic and aliphatic CH stretching vibrations and the bands observed at ~ 1600 cm^{-1} indicate the presence of the aromatic ring C=C stretching band (Table 5).

The characteristic chemical shifts of the ^{1}H NMR spectral data of the α-amino nitrile (5) (Figure 1) are the cyclic methylene protons (10H) at the range 1.75 and 2.35 ppm, a singlet at 4.4, 1H for NH and aromatic protons at 6.8 t for Ha (1H), at 7.3 m for Hb and Hc (2H) and at 7.5d for Hd (1H).

The α-Amino amides listed in table (2) were prepared from the hydrolysis of the α-amino nitriles with

90% sulfuric acid by heating the mixture on a steam bath .

The characteristic bands of the α-amino amides (8-14) are listed in table (6) having NH band at 3460-3420 cm^{-1}, NH_2 bands at 3390-3240 cm^{-1}, CH aromatic at 3480-3010 cm , CH aliphatic at around 2990-2870 cm^{-1}, amide I absorption due to C=O, near 1650 cm^{-1} and amide II band due to NH_2 deformation mode in primary amides at 1580cm $^{-1}$.

^{1}H NMR spectrum (Figure 2) for amide (4) showed the following chemical shifts : the cyclic methylene protons (10H) at the range 1.2 - 2 ppm; NH proton as a singlet at 4.65 ppm, 1H; NH_2 protons at 5.4 ppm, s, 1H, NHa and 6.4 ppm, s, 1H, NHb; and aromatic protons as a pair of doublets for p-disubstitution at the region 6.7 ppm for Hc, 2H and at 8.0 ppm for Hd, 2H.

Treatment of the previously prepared amides (9-12) with p-bromophenancyl bromide gave the desired oxazole derivatives (table 3).

The IR spectra of the prepared oxazoles (Table 7) have the following characteristic bands: NH band at 3440-3360 cm^{-1}; C–H aromatic as weak band just above 3000 cm^{-1} and C–H aliphatic at about 2980-2940 cm^{-1}; a band at 1650-1580 cm^{-1} due to C=C and C=N vibrations; a strong band at the range 1080-1020 cm^{-1} due to =C–O–C=; and bands appearing in the region 900-700 cm^{-1} attributed to aromatic C–H out-of-plane deformation vibrations.

Structure of compound (16) was confirmed by it's ^{1}H NMR spectrum (Figure 3). The following spectral data has been observed: cyclic methylene peaks at the range 1.7-2 ppm (10H); a singlet at 3.85ppm for OCH_3 (3H); a singlet at 4.8ppm for NH (1H); aromatic peaks at 6.3 ppm, t for Ha (1H), at 6.7 ppm, m for Hb and Hc in addition to the oxazole proton as doublet at 6.8 ppm, for Hd (1H); and aromatic protons at 7.7 ppm and 8.2 ppm for (4H) as a pair of doublets for the p-disubstituted benzene.

The 4-oxazolone derivatives (Table 4) were obtained by treatment of the α-amino amides (8, 10, 11, 14) with α-chloroacetic acid. 4-Hydroxy oxazole was first formed as shown by TLC, and as reflux continued a second lower spot appeared, which indicated the formation of the non-aromatic ozolone form. When reflux was continued the intensity of the lower spot increased indicating that the keto form is dominated [15] as in compound 21.

Characteristic bands of IR spectra of 4-oxazolones (19-22) are listed in table (8). These include bands due to OH stretching at 3480-3440 cm^{-1} for the enol form; NH band at ν = 3390-3280cm^{-1}; C–H aromatic as strong band above 3000 cm^{-1}, and C–H aliphatic at about 2900-2820 cm^{-1}; bands due to C=O vibration at 1740-1680 cm^{-1}; and bands at 1590-1500 cm^{-1} due to C=C and C=N vibration.

The structure of 4-hydroxy oxazole (19) was confirmed by its ^{1}H NMR spectrum (Figure 4). The characteristic chemical shifts are the cyclic methylene protons at the range 1.2-2.0 ppm (10H), CH_3 protons at 2.3 ppm (3H), NH as a broad peak at 4 ppm (1H), OH as a broad peak at 5.3 ppm(1H), the oxazole proton at 6.8 ppm (1H), and aromatic protons at the range 6.5-7.1 ppm (4H).

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الخلاصة

تضمن البحث تحضير مشتقات الاوكسازول و 4–اوكسازولون ابتداءا من الفا–امينونتريلات. وقد تم ذلك من خلال تحضير الالفا–امينونتريلات حسب طريقة ستريكر المطورة، عند معاملة الالفا–امينونتريلات مع حامض الكبريتيك 90% على حمام بخاري لمدة عشرة دقائق تم الحصول على الالفا–امينوامايد الذي تم مفاعلته مع بارا–بروموفنانسيل بروميد للحصول على مشتقات الاوكسازول، ومع كلورو حامض الخليك للحصول على مشتقات 4–اوكسازولون.

Table 1. Melting points and percent yield of the prepared α-aminonitriles

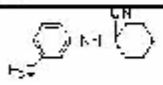
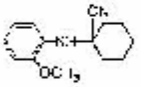
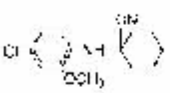
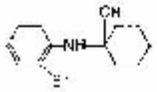
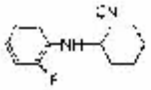
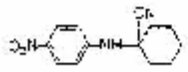
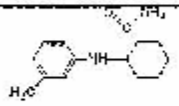
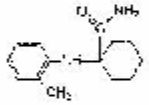
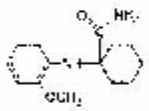
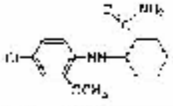
Amine Used	Ketone Used	α-Aminonitrile	Structure	Compd. No.	M.P. °C	% Yield
o-Toluidine	Cyclohexanone	N-(2-Methyl phenyl)-1-cyano cyclohexyl-amine		1	83-85	90
o-Toluidine	Cyclohexanone	N-(2-Methyl phenyl)-1-cyano cyclohexyl-amine		2	58-60	85
o-Anisidine	Cyclohexanone	N-(2-Methoxy phenyl)-1-cyano cyclohexyl-amine		3	81-83	95
4-Chloro-2-anisidine	Cyclohexanone	N-(4-Chloro-2-methoxy phenyl)-1-cyano cyclohexyl amine		4	95-97	80
o-Bromo aniline	Cyclohexanone	N-(2-Bromo phenyl)-1-cyano cyclohexyl-amine		5	87-89	85
o-Fluoro aniline	Cyclohexanone	N-(2-Fluoro phenyl)-1-cyano cyclohexyl-amine		6	42-44	70
p-Nitro aniline	Cyclohexanone	N-(4-Nitro phenyl)-1-cyano cyclohexyl amine		7	190-192	82

Table (2): Melting points and percent yield of the prepared α-aminoamide

α-Aminonitrile used	α-Aminoamides	Structure	Compd. No.	M.P. °C	% Yield
1	N-(3-Methyl phenyl)-1-carbamoyl cyclohexyl-amine		8	119-120	87
2	N-(2-Methyl phenyl)-1-carbamoyl cyclohexyl-amine		9	90-92	90
3	N-(2-Methoxy phenyl)-1-carbamoyl cyclohexyl amine		10	148-150	89
4	N-(4-Chloro-2-methoxy phenyl)-1-carbamoyl cyclohexyl-amine		11	145-146	80

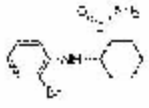
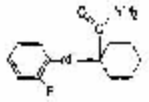
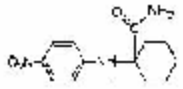
5	N-(2-Bromo phenyl)-1-carbomoyl cyclohexyl amine		12	120-122	60
6	N-(2-Fluoro phenyl)-1-carbomoyl cyclohexyl amine		13	91-93	60
7	N-(1-Nitro phenyl)-1-carbomoyl cyclohexyl amine		14	211-213	70

Table (3): Melting points and percent yield of the prepared Oxazoles.

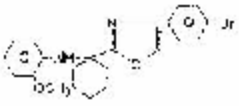
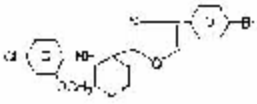
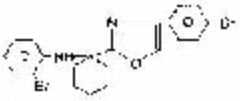
o Amino amide used	Oxazole	Structure	Compd. No.	M.P. °C	% Yield
9	1-[4-(*P*-Bromo phenyl)-oxazole-2-yl]-N-(2-methyl phenyl)-cyclohexyl amine		15	88-90	50
10	1-[4-(*P*-Bromo phenyl)-oxazole-2-yl]-N-(2-methoxy phenyl)-cyclohexyl amine		16	140-142	45
11	1-[4-(*P*-Bromo phenyl)-oxazole-2-yl]-N-(4-chloro-2-methoxy) cyclohexyl amine		17	135-137	40
12	1-[4-(*P*-Bromo phenyl)-oxazole-2-yl]-N-(2-bromo phenyl)-cyclohexyl amine		18	110-112	20

Table (4): Melting points and percent yield of the prepared 4-oxazolone, 4-hydroxy oxazole.

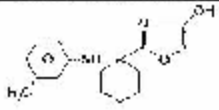
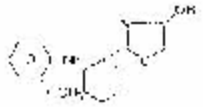
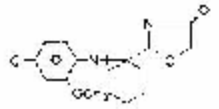
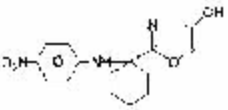
o Amino amides used	4-Oxazolone, 4-hydroxy oxazole	Structure	Compd. No.	M.P. °C	% Yield
8	2-[N-(2-Methyl phenyl)-cyclohexyl amine]-4-hydroxy oxazole		19	100-102	45
10	2-[N-(2-Methoxy phenyl)-cyclohexyl amine]-4-hydroxy oxazole		20	82-85	75
11	2-[N-(4-Chloro-2-methoxy phenyl)-cyclohexyl amine]-oxazolin-4-one		21	138-140	50
14	2-[N-(4-Nitro phenyl)-cyclohexyl amine]-4-hydroxy oxazole		22	202-204	20

Table (5): Characteristic infrared absorption bands of α-aminonitriles

Compd. no.	ν NH cm⁻¹	ν C–H cm⁻¹ Aromatic	ν C–H cm⁻¹ Cyclic	ν C≡N cm⁻¹	ν C=C cm⁻¹	δ NH cm⁻¹	γ CH cm⁻¹ out-of-plane
1	3350s	3280w, 3020m	2960w, 2920s	2205m	1595s	1510s	770s
2	3360s	3020m, 3000m	2910s, 2820s	2205w	1570s	1500m	750s
3	3380m	3060vw, 3020vw	2925s, 2830m	2230vw	1580m	1490s	740s
4	3390m	3050w	2980w, 2920m	2220vw	1580s	1490s	850m, 790m
5	3380s	3060w, 3020m	2920m, 2860m	2210w	1620s	1520s	730s
6	3368s	3060vw, 3040vw	2910s, 2840s	2210vw	1610s	1520	730s
7	3390s	3040w	2900m, 2820m	2205w	1580s	1520m	820s

Table (6): Characteristic infrared absorption bands of α-aminoamides

Compd. no.	ν N–H cm⁻¹	ν NH₂ cm⁻¹	ν C–H cm⁻¹ Aromatic	ν C–H cm⁻¹ Aliphatic, cyclic	Amide I Band C=O cm⁻¹	Amide II NH₂ deformation cm⁻¹
8	3460s	3325s, 3310s	3010m	2910s, 2820m	1550s	1560s
9	3440m	3360vw, 3250s	3020w	2900s, 2840m	1650s	1570s
10	3450s	3280w, 3190s	3030vw	2980w, 2830vw	1655s	1590m
11	3420s	3280m, 3200m	3040vw	2900w, 2840m	1640s	1580s
12	3420m	3290w, 3250vw	3040vw	2910vw, 2840w	1640s	1580w
13	3420s	3280m, 3240s	3080vw	2990m, 2840m	1650s	1590s
14	3440m	3300m, 3180w	3100vw	2910m, 2840w	1655s	1560s

Table (7): Characteristic infrared absorption bands of Oxazole

Compd. No.	ν N–H cm⁻¹	ν C–H cm⁻¹ Aromatic	ν C–H cm⁻¹ Aliphatic or cyclic	ν C=C or ν C=N cm⁻¹	ν C–O–C cm⁻¹	Aromatic δ out-of-plane deformation
16	3400s	3140s	2900s – 2820m	1650s, 1580s	1200s	830m, 750w
16	3400w	3060w	2980w – 2940m	1680s, 1580s, 1590m	1180s	800s, 700m
17	3360bw	3080w	2910m	1680, 1580	1200s	850s, 790m, 720m
18	3400w	3060w w	2920w	1680s, 1580s	1190s	800s, 720m

Table (8): Characteristic infrared absorption bands of 4-oxazolone, 4-hydroxy oxazole

Compd. no.	ν OH cm⁻¹	ν NH cm⁻¹	ν C=O cm⁻¹	ν C–H cm⁻¹ Aromatic	ν C–H cm⁻¹ Aliphatic or cyclic	ν C=C, ν C=N cm⁻¹
19	3460s	3360s	1720s	3020s	2900s, 2820s	1680s, 1540s
20	3460s	3360s	1680s	3140s	2900s, 2820s	1580s, 1500m
21	-	3390s	1730	3150s	2850s, 2840m	1650s, 1500m
22	3400s	3280s	1740s	3160s	2900s, 2820m	1570s, 1510w

* Compounds 19, 20 and 22 were obtained as a mixture of the two tautomers, while compound 21 was obtained as the keto form.