Synthesis and Antibacterial Evaluation of 2-(chloro / ethyl thio / seleno)-1,8-naphthyridine-3-azetidine Derivatives

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Abstract

Synthesis of new heterocyclic fuse compounds by reaction of N-acetyl-2-amino pyridine with through Vilsmeier-Haack cyclization to give 2-chloro-3-formyl-1,8-naphthyridine (1) , chloro atom changing with selenium (2) or Et-S- group (3) , the formyl group in the compounds (1,2,3) converted to schiff base by react with aryl amine (4-9), shiff base derivatives reaction with chloroacetylchloride in triethylamine to give azetidine ring (10-15) . The structures of synthesized compounds were confirmed by spectral and physical data. Some of the newly synthesized compounds exhibited antibacterial activity.

Keywords: schiff base , 1,8-naphthyridine , azetidine , organoselenium compounds , Vilsmeier-Haack.

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تحضير ودراسة الفعالية البايولوجية لمشتقات 2-(كلورو / اثيل ثايو / سلينو)-8,1-نفثايريدين-3-ازيتيدين

مهند يقظان صالح العلاف

قسم الكيمياء - كلية التربية للعلوم الصرفة - جامعة الموصل

الخلاصة

تم تحضير مركبات حلقية غير متجانسة جديدة من تفاعل مركب اسيتايل -2-امينو بريدين مع كاشف فلزماير- هوك لنحصل على 2-كلورو-3-فورمايل-8،1-نفثايريدين (1) ، تم استبدال ذرة الكلور في الموقع 2 بذرة سيلينيوم (2) او مجموعة اثيل ثايول (3) ، حلقة النفثايريدين الحاملة لمجموعة فورميل (3،2،1) حولت مجموعة الالديهايد الى قواعد شيف بمفاعلتها مع امين اروماتي (4-9) وتم مفاعلة قواعد شيف الناتجة الى حلقة الازيتدين (10-15) بمفاعلتها مع كلورو-كلوريد حامض الخليك بوجود قاعدة قوية . شخصت المركبات المحضرة بااستخدام الطرق الفيزياوية والطيفية ، وجرت دراسة الفعالية البايولوجية لبعض المركبات المضرة على بعض انواع البكتريا .

الكلمات المفتاحية : قواعد شيف ، 8،1-نفثايريدين ، ازيتيدين ، مركبات السلينيوم العضوية ، فالزماير-هاك .

Introduction

Many organic compounds have contains 1,8-naphthyridine skeleton are vary important compounds , as antimicrobial (Gemiflloxacin)which have naphthyridine[1], drug[2], anticonvulsants[3], antipertensives[4], antibacterial[5] and many derivatives used for treatment of memory disease[6], and being exploited in cancer chemotherapy[7], metal selenide injection in naphthyridine to give organo-metal[8], 1,8-naphthyriden have been reported medicinal application in the study of bioorganic and bioorganometalic processes and application[9,10]. Naphthyridine computational calculation study of Naphthyridine gave good result of the tautomeric[11] importance on the determination of compounds properties and the area of application theoretical point of view the structures and vibration properties[12]. Many important methods have been to synthesis naphthyridine nuclear as : Vilsmeier-Haack reagent[13], Skraup and Friedlander reaction[14] used synthesized quinolines and

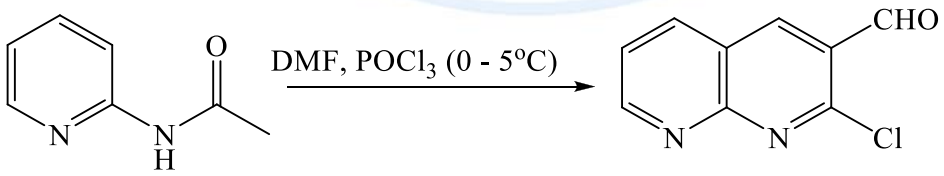
naphthyridiens , Baylis-Hillman adducts [15] is a useful method, other method Friedlander reaction used synthesis pyridines , quinolines , naphthyridines[16]. Selenoanphthyridines synthesis by reacting 2-chloro-3-carboxyldehyde-1,8-naphthyridine with sodium hydrogen selenide has given introduction selenium in organic molecules[17]. Naphthyridine use as ligands inorganic reactions to give new complexes , finally, Schiff bases carry out by reacting carbonyl group in naphthyridine with amino groups[19,20] and treated with chloroacetylchloride convert to azetidine ring[21-24].

Experimental

Melting point were recorded on electro-thermal CIA9300 melting point apparatus and are uncorrected, ^{1}HNMR spectra were recorded on nucleic magnetic resinous model ultra-shield 300MHz , Bruker Co ., Germany , using TMS as internal reference and DMSO-d6 as solvent . IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, by using KBr discs.

Synthesis of 2-chloro-3-formyl-1,8-Naphthyridine (1)[25]

To solution of (0.01mole) of N-(pyridine-2-yl) acetamides in (0.15 mole) dry DMF with stirring $POCl_3$ (0.06mole) at (0-5^{o}C) was added drop wise. The reaction mixture was heated at 80C for about 16 hrs with stirring. The reaction mixture was poured into crushed ice and the precipitated solid was filtered and washed with excess of cold water and dried and re-crystallized from ethyl alcohol. The Physical Constant and chemical and spectra data of compound are given in Table 1 and 2.



Scheme-1- synthesis of 2-chloro-3-formyl-1,8-Naphthyridine

Synthesis of 3-formyl-2-seleno-1,8-Naphthyridine (2)[26]

A mixture 2-chloro-3-formyl-1,8-naphthyridine (1.91 g, 1 mmol) and freshly prepared solution of sodium hydrogen selenide were taken in a round bottom flask in ethanol (20 ml).

The reaction mixture was refluxed for 2–3 hrs , cooled, the reaction mixture was poured in to crushed ice and made acidified with dil (4N HCl). The product was filtered and washed with water, dried, recrystallized from alcohol. The Physical Constant and chemical and spectra data of compound are given in Table 1 and 2 .

Synthesis of 3-formyl-2-ethylthio-1,8-Naphthyridine (3)[21]

To a solution of compound (1) (1mmole) in (5 ml) dry DMF, (5ml), sodium sulphide (1.5mmole) was added and stirred for 4hrs. at room temperature, then the corresponding halo compound was added and stirred for another 1 hr. and poured in to ice-cooled water. The precipitate obtained was filtered dried and re-crystallized from ethanol. The physical constant and chemical and spectra data of compound are given in table 1 and 2 .

Synthesis of N-(2-substituted-1,8-Naphthyridine-3-yl methylene) – N – aryl imine (4-9)[27]

To a solution of compounds (1,2,3) (1m.mole) in ethanol (5 ml) was added with stirring aryl amine (2m.mole), and the mixture was refluxed for 4hrs. On cooling, the precipitate was formed, filtered off, washed with ethanol and cold water, dried and re-crystallized from ethanol. The physical constant and chemical and spectra data of compound are given in Table 1 and 2 .

Synthesis of 3-chloro-4(2-substituted-1,8-Naphthyridine-3-yl)-1-aryl–azetidine-2-one (10-15)[21]

The compound (4-9) (0.01 mol) was dissolved in dry DMF (20 ml) and tri-ethylamine (0.02 mol) was added to it. Chloroacetyle chloride (0.02 mol) was added drop wise for a period of 30 min. The reaction mixture was refluxed for 6 hrs. Then poured into crushed ice, the resulting solid was filtered washed with cold water and re-crystallized from ethyl acetate. The physical constant and chemical and spectra data of compound are given in Table 1 & 2 & 3 .

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Table 1: Physical Constant of Compound (1-15)

Comp. no.	R	m.p °C	Color	Yield %	Formula
1	---	165-167	Pale yellow	64	$C_9H_5N_2OCl$
2	---	133-136	Red	88	$C_9H_6N_2OSe$
3	---	109-111	Yellow	67	$C_{11}H_{10}N_2OS$
4	$-CH_3$	188-190	Brawn	54	$C_{16}H_{12}N_3Cl$
5	$-OCH_3$	193-194	Pale brawn	58	$C_{16}H_{12}N_3OCl$
6	$-CH_3$	235-236	Dark brawn	66	$C_{16}H_{13}N_3Se$
7	$-OCH_3$	228-230	Dark brawn	61	$C_{16}H_{13}N_3SeO$
8	$-CH_3$	205-207	Red	74	$C_{18}H_{17}N_3S$
9	$-OCH_3$	198-200	Brawn	69	$C_{18}H_{13}N_3SO$
10	$-CH_3$	231-235	Dark brawn	79	$C_{18}H_{13}N_3Cl_2O$
11	$-OCH_3$	228-229	Pale red	76	$C_{18}H_{13}N_3Cl_2O_2$
12	$-CH_3$	252-255	Orange	58	$C_{18}H_{14}N_3ClO$
13	$-OCH_3$	261-262	Dark red	55	$C_{19}H_{14}N_3ClO_2$
14	$-CH_3$	234-235	Pale brawn	45	$C_{20}H_{18}N_3SO$
15	$-OCH_3$	242-245	Black	57	$C_{20}H_{18}N_3SO_2$

Table (2): IR spectral (KBr, v, cm-1) of compound (1-15)

Comp No.	C=O	C=N	C-H (aldehyde)	C-H (aromatic)	NH	Other
1	1720	1590	2780	3050	----	775C-Cl
2	1690	1595	2790	3070	3241	1636 C=Se
3	1696	1590	2775	3040	----	1198-1086 C-S-C
4	----	1645	----	3052	----	670 C-Cl
5	-----	1625	----	3045	----	745C-Cl
6	----	1605	----	3055	3328	1666C=Se
7	----	1595	----	3100	3298	1650C=Se
8	----	1652	----	3025	----	1210-1085 C-S-C
9	----	1623	----	3050	----	1189-1065 C-S-C
10	1752	1634	----	3035	----	745C-Cl
11	1753	1655	----	3045	----	760C-Cl
12	1753	1634	----	3060	3246	1695C=Se
13	1719	1637	----	3100	3315	1670C=Se
14	1703	1655	----	3035	----	755C-Cl
15	1750	1605	----	3038	----	750C-Cl

Table 3: ^{1}H NMR data of compound (10-15)

Compound No.	^{1}H NMR (δ, ppm) – DMSO-d6
10	7.41(1H, t, C-6-H), 7.85 (1H, d, C-5-H), 8.56(1H, d-C-4-H), 8.78(1H, m, C-7-H), 5.82(1H, d, CH-Cl) , 6.95(1H, d, CH-N), (7.2-7.35) (4H, m, Ar-H), 2.4 (3H, s , CH_3-Ar)
11	7.40(1H, t, C-6-H), 7.80 (1H, d, C-5-H), 8.52(1H, d, C-4-H), 8.72(1H, m, C-7-H) , 5.84(1H, d, CH-Cl), 6.92(1H, d, CH-N) (7.15-7.33) (4H, m, Ar-H), 3.10(3H, s, Ar-OCH_3)
12	9.05(1H, s, N-H),7.40(1H, t, C-6-H), 7.80 (1H, d, C-5-H), 8.52(1H, d, C-4-H), 8.72(1H, m, C-7-H), 5.88(1H, d, CH-Cl), 6.92(1H, d, CH-N) (7.13-7.33) (4H, m, Ar-H), 2.44(3H, s, Ar-CH_3)
13	9.15(1H, s, N-H),7.44(1H, t, C-6-H), 7.76 (1H, d, C-5-H), 8.50(1H, d, C-4-H), 8.88(1H, m, C-7-H), 6.01(1H, d, CH-Cl), 6.78(1H, d, CH-N) (7.18-7.39) (4H, m, Ar-H), 3.04(3H, s, Ar-OCH_3)
14	7.51(1H, t, C-6-H), 7.59 (1H, d, C-5-H), 8.61(1H, d-C-4-H), 8.78(1H, m, C-7-H), 5.56(1H, d, CH-Cl) , 6.76(1H, d, CH-N), (7.17-7.35) (4H, m, Ar-H), 2.47 (3H, s , CH_3-Ar), 2.94(2H, q , S-CH_2) , 1.42(3H , t , -CH_3)
15	7.28(1H, t, C-6-H), 7.66 (1H, d, C-5-H), 8.46(1H, d-C-4-H), 8.82(1H, m, C-7-H), 5.60(1H, d, CH-Cl) , 6.64(1H, d, CH-N), (7.36-7.55) (4H, m, Ar-H), 2.25 (3H, s , CH_3-Ar), 2.81(2H, q , S-CH_2) , 1.37(3H , t , -CH_3)

Result and Discussion

Although many routes have been developed for functionalized 1,8-naphthyredine[28,29,30]. The Vilsmeier approach is found to be among the most efficient for achieving useful transformation and hetero annulations. Thus in this communication we reported the synthesis of 2-chloro-3-formyl-1,8-Naphthyridine from the reaction of N-(pyridin-2-yl) acetamide with Vilsmeier reagent and transformation of 2-chloro and 3-formyl groups into different functionalities. The Vilsmeier cyclization of N-(pyridin-2-yl) acetamide was carried out by adding $POCl_3$ to the substrate in DMF at (0-5^{o}C) following by heating to (90^{o}C) to afford 2-chloro-3-formyl-1,8- Naphthyridine. The mechanism of reaction fallow (scheme 2)[21]

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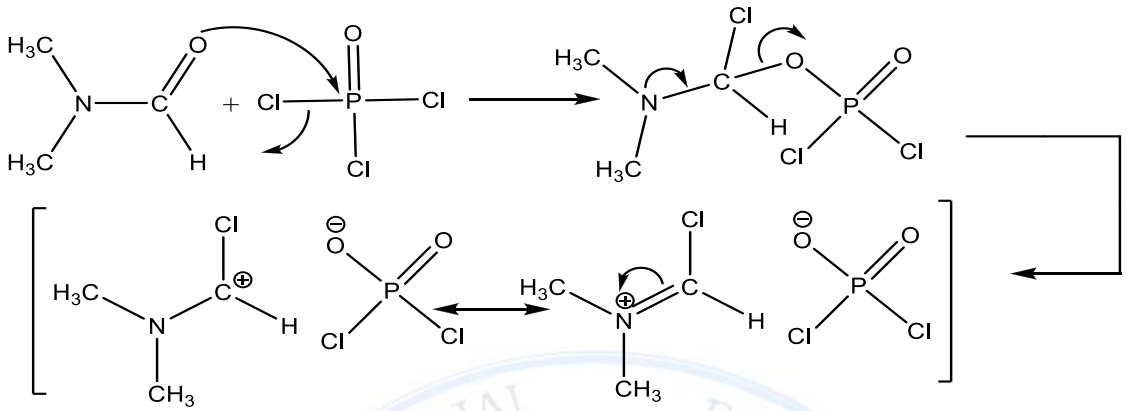


Scheme-2- the mechanism of Vilsmeier-Haack transition

The structures of Synthysized compounds were elucidated by mean of physical data (Table 2) . the IR spectra of compound (1) showed a sharp and many absorption at 1720 cm^{-1} for the carbonyl of aldehydic group and absorption at 2780 cm^{-1} for proton of aldehydic group and absorption at 775 cm^{-1} for C-Cl group.

Selenium reacts quickly with sodium borohydride in aqueous solution to produce sodium hydrogen selenide vigorously and isothermally the reaction equation[17] that is:

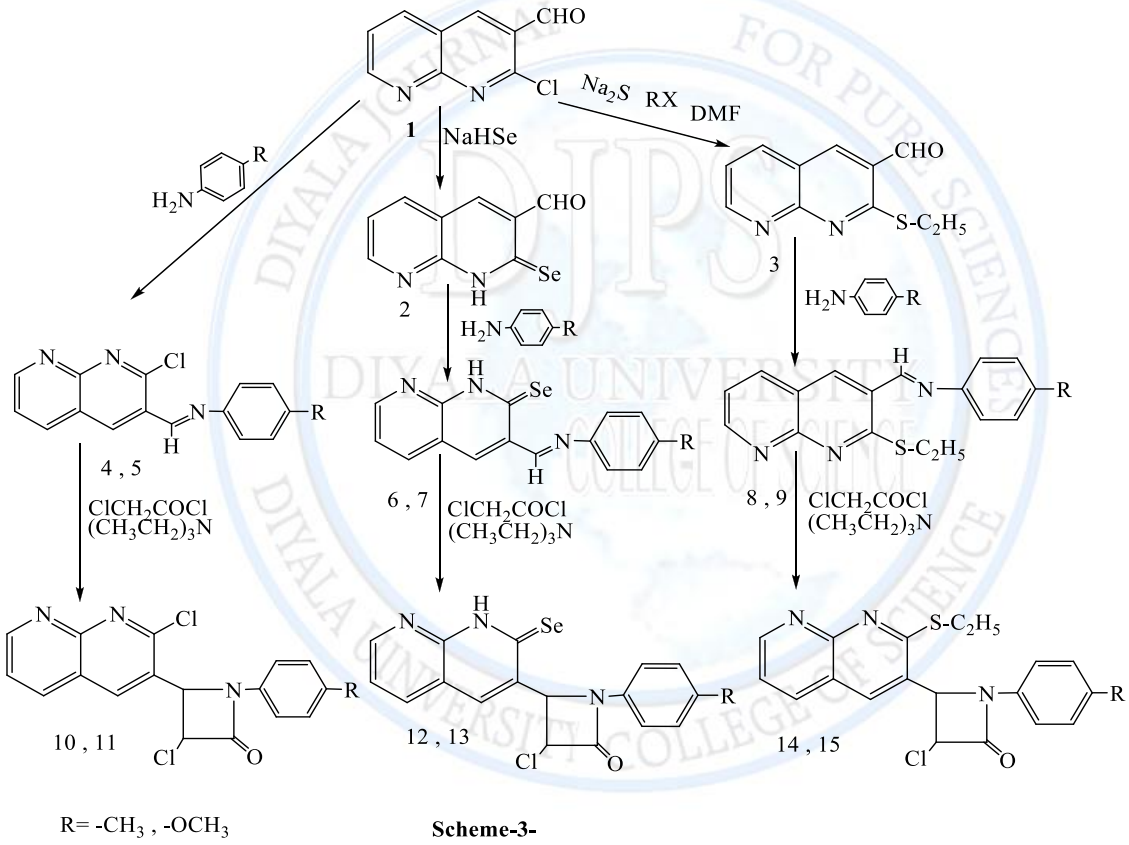
$$4\ NaBH_4 + 2\ Se + 7\ H2O \rightarrow 2\ NaHSe + Na_2B_4O_7 + 14\ H_2$$

Sodium hydrogen selenide substituted chloro group in naphthyridine to selenium organic compound (2). The IR spectrum of compound (2) in Tale (2) showed absence of the characteristic absorption in IR for C-Cl bond which is present in the IR spectrum of compound (1) and presence of strong stretching absorption at 1636 cm^{-1} for C=Se group .

The reaction of compound (1) with Na2S/DMF followed by reaction with ethyl chloride afforded a thioether derivative (3). The IR spectrum of compound (3) in Tale (1) showed absence of the characteristic absorption in IR for C-Cl bond which is present in the IR spectrum of compound (1) and presence of strong absorption at 1198-1086 cm^{-1} for C-S-C.

The reaction of compounds (1,2,3) with aryl amine can afford schiff-base derivatives (4,5,6,7,8,9) of 1,8-Naphthyridine. The formation of compounds (4,5,6,7,8,9) was supported by absence of the characteristic absorption in IR for aldehydic group which is present in the IR spectrum of compound (1,2,3) show in table 2 .

The substituted Schiff- base derivatives (4,5,6,7,8,9) were also reacted with chloro acetylchloride in the presence of triethylamine which act as a catalyst undergoes cyclisation to give 1,8-Naphthyridine azetidine-2-one derivatives (10,11,12,13,14,15). The formation of compound (10,11,12,13,14,15) was supported with spectroscopic data spectroscopy by showing the absence of the –CH-Cl at δ(5.56-6.01) and –CH-N at δ(6.64-6.95) in the ^{1}HNMR spectra and presence of strong absorption at about (1703-1753) cm^{-1} in the IR for C=O on the azetidine ring. And other signal IR spectroscopic data and ^{1}HNMR spectra in table (2&3)



Scheme-3-

Biological Active

the biological studies of compounds (**10-15**) were evaluated against *(Eschershia Coli , Proteus Vulgaris , Staphylococcus Epidermidis , Staphylococcus Areus)* table (4) the results showed that these compounds (**10-15**) have a good activity against (Staph Aureus and Staph Epidermidis).

Table (4) : Antibacterial activity data of compound (10-15)

Compound No.		Zone of inhibition in mm			
		Staph Aureus	Staph Epidermidis	E. Coil	Proteus Vulgaris
		10 mg/disk	10 mg/disk	10 mg/disk	10 mg/disk
10		16	19	14	9
11		15	22	11	10
12		22	26	23	19
13		24	25	21	20
14		16	14	14	15
15		17	16	16	13
Control	Ciprofloxacin 5mg/disk	-	-	15	14
	Chloramphenicol 30mg/disk	17	16	14	-

Conclusion

We have developed a simple and efficient method for the synthesis of some new 1,8-naphthyridine derivatives and organic selenium compounds and azetidine which uptake very important compounds cause the stricture of drag contain it , characterized by spectral techniques . The new synthesized compounds (10,11,12,13,14,15) were evaluated for antibacterial activities. The results obtained indicated that these compounds have a good activity against (Staphylococcus aureus and Staphylococcus epidermidis).

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