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SYNTHESIS, IDENTIFICATION AND ANTIBACTERIAL EVALUATION OF SOME 1,3,4- OXADIAZOLES DERIVATIVE ON 1,8-NAPHTHYRIDINE RING

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ABSTRACT

Several 1,8-naphthyridine derivative were prepared using Vilsmeier-Haack synthization. 2-chloro-3-formyl-1,8-naphthyridine was synthesized by reacting N-(pyridin-2-yl) acetamide with $POCl_3$ in dimethylformamide. 1,8-naphthyridine group was oxidized with NIS-K_2CO_3 in methanol at room temperature to yield 2-chloro-3-methoxy carbonyl -1,8-naphthyridine (2), acid hydrazide was then prepared by treating the methyl ester with hydrazine hydrate in ethanol (3), the synthesis of 2-chloro-3[2(1,3,4-oxadiazol-5-thiol-1,8-naphthyridine (4) was obtained from compound(3) reaction with CS_2 in basic medium, acid hydrazide was then converted to the corresponding carbothioamide (5) by treating with benzyl isothiocyanate respectively. Thiosemicarbazide (5) was reacted with mercuric oxide in methanol to produce 1,3,4-oxadiazole (6). 2-chloro-3-[2(1,3,4-oxadiazole)]-1,8-naphthyridine (8) was yielded from acid hydrazide reaction with formic acid followed by PbO_2. Acid hydrazide (3) was treated with benzaldehyde to formhydrazone (9) which then reacted with PbO_2 to give 1,3,4-oxadiazole (10). Finally. The structures of synthesized compounds were confirmed spectroscopically using IR and ^{1}HNMR in addition to another physical data. The newly synthesized compounds (4,6,8,10) show a significant antibacterial activity.

KEYWORDS: heterocyclic compounds, Vilsmeier-Haack, 1,8-naphthyridine, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-trazole.

INTRODUCTION

The importance of 1,8-naphthyridine derivatives have been come from the present of 1,8-naphthyridine skeleton in many compounds that have been isolated from natural substance.[1,2] Also,several 1,3,4-oxadiazole derivatives have been reported and showed a significant biological activities.[7,8] Both 1,2,4-triazole and 1,3,4-thiadiazole have been a great deal of discussion due to their various pharmacological properties such as anti-inflammatory, analgesic, anti-microbial and anti-tumoral activities.[5,6] One of the most wide use of 1,8-naphthyridine derivative is 2-amino-N-hydroxy-1,8-naphthyridine-3-carboxamidine which is used for selective control of weeds in barley, wheat, maize, sorghum and rice.[3] Also, it is well known that 3-phenyl-1,8-naphthyridine has the ability to contain different kind of chemical group such aspiperidyl, piperazinyl, merpholinylor an N-dictuanolumine side chain. These compounds were shown a significant activity as inhibitor of human platelets aggregation which induced by arachidonate and collagen.[4]

As it well known, the hydrazones group plays an important role for their antimicrobial activity. Therefore, a number of hydrazoneshydrazine have interesting behavior as an anti-bacterial and anti-fungal[9,10], anti-inflommetory[11,12], anti-malarial.[13] The synthesized hydrazide hydrazones derivatives were used in a series of heterocyclic transformation to give 1,3,4-oxadiazole, 1,2,4-triazole and 1,3,4-thiadiazole.[14,15,16] Consequently, the aim of this study is to obtaining new hydrazide hydrazones derivatives with such wide spectrum of pharmaceutical applications.

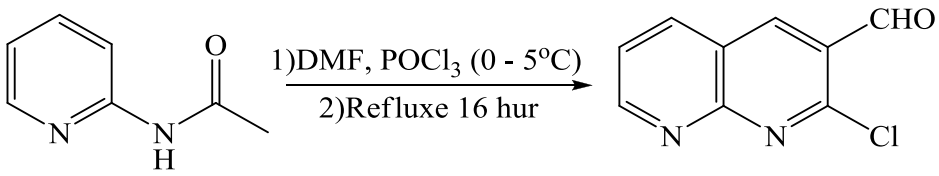
EXPERIMENTAL

^{1}HNMR spectra has been recorded on nucleic magnetic resinous model300MHz Bruker Co., Germany using TMS as internal reference and DMSO-d6 as solvent. Infrared Spectrophotometer Model Tensor 27, Bruker Co. Germany was used to record IR spectrausingKBr discs.Melting point data were collected by using electro-thermal CIA9300 melting point apparatus.

Synthesis of 2-chloro-3-formyl-1,8-Naphthyridine (1)[17]

To mixture of (0.01mole) of N-(pyridine-2-yl) acetamides in (0.15 mole) dry DMF,$POCl_3$ (0.06mole) at (0-5^{o}C) was added drop wise with stirring reaction for about 16 hrs. The reaction solution was then poured into crushed ice and the precipitated solid was filtered and washed with excess of cold water.The final result then dried and re-crystallized from ethyl

alcohol. The melting points is (165-198^{o}C) with 60% yield. The chemical and spectra data of compound (1) are shown in table 2 and 3.



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

Synthesis of 2-chloro-3-methoxycarbonyl-1,8-Naphthyridine(2)[18]

NIS (N-iodosuccimide) (0.025mole) and potassium carbonate (0.025mole) were added to a solution of 2-chloro-3-formyl-1,8-Naphthyridine (0.01mole) in methanol (10 ml). The resultant dark mixture was stirred in dark for 4 hrs. The reaction mixture was then diluted with 5-6 ml of water. (0.5 g) of sodium thiosulphite was added to remove any remaining NIS or hypoiodite species and the solid product filtered, dried and re-crystallized from ethanol. The melting point was 82-83^{o}C with 65% yield. The chemical and spectra data of the compounds (2) are given in table 2 and 3.

Synthesis of 2-chloro-1,8-Naphthyridine-3-hydrazide (3)[19]

To (0.01 mole)of compound (2) in ethanol, hydrazine hydrate (6.5 ml) was added. The reaction mixture was stirred for 10 hrs at temperature below 100^{o}C. The next step was evaporated the reaction mixture to half under reduced pressure. The precipitate was then separated in cooling medium, collected by filtration and then re-crystallized from ethanol. The melting point was (171-173^{o}C) with 60% yield. The chemical and spectra data of the compound (3) are given in table 2 and 3.

Synthesis of 2-chloro-3-[5-(1,3,4-oxadiazolo-2-thione)]-1,8-Naphthyridine (4)[19]

Ethanolic solution of hydrazide (3) (1.0mmole) was added to potassium hydroxide (0.056g, 1.0m mole) and carbon disulfide (2m mole). The mixture then heated under reflux until the hydrogen sulfide evolution ceased. The solvent was then removed and solution was filtered off by adding water. The filtrate was acidified with diluted hydrochloride acid. The precipitate formed was collected washed with water and crystallized from ethanol. The melting point was (212-215^{o}C) with 45% yield. The chemical and spectra data of the compound(4) are given in table 2 and 3.

Synthesis of2-chloro-3-[4-phenyl-1-acetyl thiosemicarbazide]-1,8-Naphthyridine(5)

Ethanolic solution of hydrazide (3)(0.01 mole) was mixed with phenyl isothiocyanate(0.02 mole) and concentrated hydrochloric acid (2 ml) and then stirred for 10 hrs at temperature below 100^{o}C. The solvent was evaporated under reduced pressure and the residue was poured on crushed ice with stirring to gain the final result. The solid formed filtered and re-crystallized from ethanol. The melting point was (252-254^{o}C) with 60% yield. The chemical and spectra data of the compound (5) are given in table 2 and 3.

Synthesis of 2-chloro-3-[5-(2-phenyl amine-1,3,4-oxadiazole)]-1,8-Naphthyridine(6)

Mercuric oxide (2.4 g, 0.01 mole) was added to solution of compound (5) (0.01 mole) in (30 ml) of methanol. The mixture was refluxed for 8 hrs and filtered while the solution is hot.The solvent was evaporated to give solid product which was dried and recrystallized from ethanol. The melting point was (273-275^{o}C) with 55% yield. The chemical and spectra data of the compound (6) are given in table 2 and 3.

Synthesis of 2-chloro-N-formyl-1,8-Naphthyridine-3-carbohydrazide (7)[13]

Acid hydrazide (3) (0.01 mole) in (20 ml) of ethanol was mixed with formic acid (0.246 g, 0.01 mole) in ethanol (20 ml) and refluxed for 6 hrs. The mixture was cooled and solid filtered, dried and recrystallized from ethanol. The melting point was (221-223^{o}C) with 50% yield. The chemical and spectra data of the compound (7) are given in table 2 and 3.

Synthesis of 2-chloro-3-(1,3,4-oxadiazol-2-yl) -1,8-Naphthyridine (8)

A homogenous solution of carbohydrazide (7) (0.01 mole)in glacial acetic acidwas mixed with PbO_2 (2.34 g, 0.01 mole) and stirred at 25^{o}C for 4 hrs. The reaction mixture was diluted with ice-water and left to stand for 24 hrs. The precipitate was filtered, washed well with cold water and recrystallized from ethanol. The melting point was (268-270^{o}C) with 55% yield for compound (8). The chemical and spectra data of the compound (8) are given in table 2 and 3.

Synthesis of N-benzylidene-2-chloro-1,8-Naphthyridine-3-carbohydrazide (9)

A mixture of acid hydrazide (3) (0.01 mole) and benzaldehyde (0.01 mole) in ethanol (20 ml) was refluxed for 6 hrs. The solvent was condensed and the precipitate filtered and recrystallized from ethanol. The melting point was (236-238^{o}C) with 55% yield. The chemical and spectra data of the compound (9) are given in table 2 and 3.

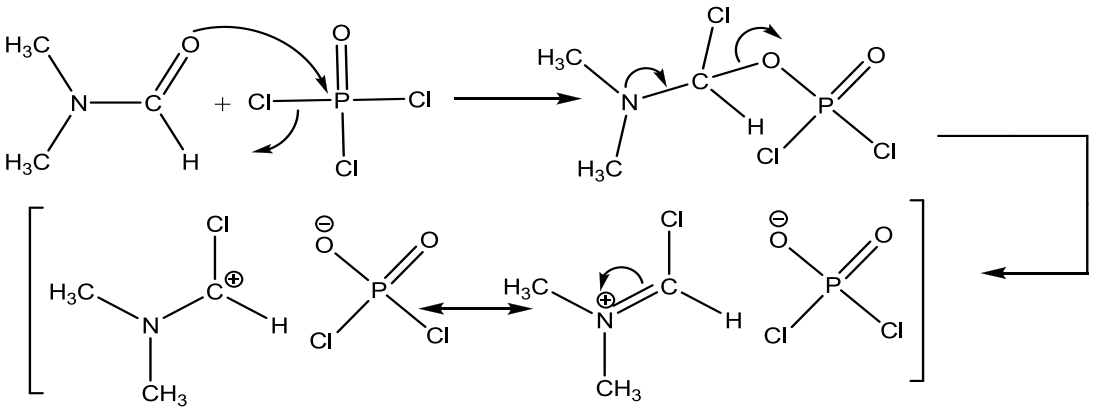
Synthesis of 2-chloro-3-(1,3,4-oxadiazol-2-yl) -1,8-Naphthyridine (10)

A homogenous solution of carbohydrazide (9) (0.01 mole)in glacial acetic acidwas mixed with PbO_2 (2.34 g, 0.01 mole) and stirred at 25^oC for 4 hrs. The reaction mixture was diluted with ice-water and left to stand for 24 hrs. The precipitate was filtered, washed well with cold water and recrystallized from ethanol. The melting point was (289-291^oC)with 50% yield for compound (10). The chemical and spectra data of the compound (10) are given in table 2 and 3.

RESULT AND DISCUSSION

Many routes have been developed for functionalized 1,8-naphthyredine.[20,21,22] However, this work shows that the Vilsmeier approach is expected to be among the most efficient for achieving useful transformations for heteroannulation reactions. Thus in this communication, the synthesis of 2-chloro-3-formyl-1,8-Naphthyridine has been reported 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^oC) following by heating to (90^oC) to afford 2-chloro-3-formyl-1,8- Naphthyridine. The mechanism of reaction fallow (scheme 2).



Scheme-2- the mechanism of Valsmeier-Haack transition

Structures of synthysized compounds were elucidated by mean of physical data (table 1). the IR spectra of compound (1) showed a sharp and many absorption at 1705 cm^{-1} for the aldehydic group and absorption at 2820 cm^{-1} for aldehydic proton and absorption at 765 cm^{-1} for C-Cl group. The ^{1}HNMR spectrum of compound (1) shows a singlet at δ 9.83 and 7.26

for aldehydic and C-H protons, doublets at δ 8.49 and 7.48 for C-7 and C-5 protons and triplet at δ 7.31 for C-6 proton.

The formyl group was oxidized to the ester group. A many the various method available.[23] The formyl group was oxidized with NIS-K_2CO_3 in methanol at room temperature to afford corresponding 2-chloro-3-methoxycarbonyl-1,8-Naphthyridine (2) in good yield (scheme 3). The IR spectra of the compound (2) showed a strong absorption at 1732 cm^{-1} for carbonyl of the ester. the ^{1}HNMR spectrum of the compound showed a singlet at δ 4.3 and 7.92 for methoxy and C-4, doublets at δ 7.42 and 8.38 for C-5 and C-7 protons and triplet at δ 7.27 for C-6 proton.

The methoxy ester (2) was treated with hydrazine hydrate in ethanol to give acid hydrazide (3). The hydrazide shows absorption at 3410 cm^{-1} for N-H and at 1680 cm^{-1} for C=O group. The ^{1}HNMR spectrum of compound (3) showed absorption a singlet at δ 9.70 for NH_2 proton and at δ 7.33,7.45, 8.01 and 8.42 for C-6, C-5, C-4, C-7 proton respectively and at at δ 9.95 for NH proton. The base catalyzed cycle condensation of hydrazide (3) with carbon disulfide give 1,3,4-oxadiazole derivative (4) in good yield under reflux condition (table 2). The synthesis of compound (5) was per formed by the reaction of compound (3) with phenyl isocyanate (scheme-3-) the products 4 and 5 were characterized by their physical and spectral data. IR spectra of these compounds showed NH stretching bands between 3380 and 3325 cm^{-1} and absorption C=O at 1695 cm^{-1} for compound (5) and absorption C=S at 1210 and 1225 cm^{-1}. In the ^{1}HNMR spectra of the compounds (4) NH protons absorption at δ 9.68 and the ^{1}HNMR spectra of the compounds (5) NH protons absorption at δ 8.85 and 10.56 ppm. as singlet. The intra molecules cyclization of compounds (5) (scheme-3-) was prefixed by basic treatment of ease intermediates under reflux conditions. thiosemicarbazide (5) with treated with mercuric oxide in methanol to give substituted 1,3,4-oxadiazole (6), The IR spectra for compound (6) shows absorption at 3380 cm^{-1} for NH and at 1605 cm^{-1} for C=N and at 1210 cm^{-1} for C-O-C. In order to synthesis mono substituted oxadiazole acid hydrazide (3) was treated with formic acid to give 2-chloro-N-formyl-1,8-Naphthyridine-3-carbohydrazide (7) which transferred to substituted 1,3,4-oxadiazole (8) by its reaction with PbO_2 (table 2) compound (7) showed absorption at 1715 cm^{-1} and 1653 cm^{-1} for C=O and band at1585 cm^{-1} for C=N and at 3380,3315 cm^{-1} for NH and at 2815 cm^{-1} for aldehydic proton. The ^{1}HNMR spectra for compound (7) showed singlet at δ 4.85 for NH and at δ 7.21-7.29 malty signals for phenyl ring and triplet signal δ 7.33 for C-6, doublet signal at δ 7.46 and 8.31 for C-5 and C-7

and signal at δ 7.81 for C-4.[24,25] Compound (7) cyclized to give 2-substituted-1,3,4-oxadiazole(8) by PbO_2. The IR spectrum of compound (8) showed absorption at 1595 cm^{-1} for C=N and at1085 cm^{-1} for C-O-C group. The ^{1}HNMR spectrum of the compound (8) appeared are the expected chemical shifts (table 2). The acid hydrazide (3) was treated with benzaldehyde to give hydrazones (9). The IR spectrum of Compound (9) showed absorption at 1675 cm^{-1} for C=O group and at 3325 cm^{-1} for NH. The ^{1}HNMR compound (9) the NH signal appeared at δ9.05 as a singlet hydrazones (9) was then cyclization to 2,5-disubstituted-1,3,4-oxadiazole (10) by PbO_2. compound (10) showed absorption at 1185 cm^{-1} for C-O-C and absorption at 1605 cm^{-1} for C=N group. The ^{1}HNMR of these compound (10) appeared at the expected chemical shifts (table 2).

The IR and ^{1}HNMR of these compound are listed in table 1 and 2.

Table 1: Physical and IR Spectral of Compound (1-10).

Comp No.	m.p	Yield %	Formula	C=O	C=N	NH	C=S	C-H (aromatic)	C-O-C	C-Cl
1	165-167	60	$C_9H_5N_2OCl$	1705	1580	----	----	3085	----	765
2	96-98	65	$C_{10}H_7N_2O_2Cl$	1732	1618	----	-----	3040	----	770
3	172-175	60	$C_9H_7N_4OCl$	1680	1620	3410	----	3035	----	775
4	212-215	45	$C_{10}H_5N_4OSCl$	----	1575	3325	1225	3085	----	775
5	252-254	60	$C_{11}H_{12}N_5OSCl$	1695	1575	3380	1220	3066	----	775
6	273-275	55	$C_{16}H_{10}N_5ClO$	---	1605	3380	----	3080	1210	778
7	221-223	60	$C_{10}H_7N_4ClO_2$	1715, 1685	1585	3380, 3315	----	3035	----	785
8	274-276	50	$C_{10}H_4N_4OCl$	----	1595	---	----	3055	1085	720
9	230-232	55	$C_{16}H_{11}N_4ClO$	1675	1605	3325	----	3035	----	775
10	268-271	50	$C_{16}H_9N_4OCl$	---	1605	----	----	3035	1125	780

Table 2: ^{1}H NMR data of compound (1-10)

Comp. No.	^{1}H NMR (ppm) – DMSO-d6
1	7.31(1H, t, C-6-H), 7.48(1H, d, C-5-H), 7.86(1H, s, C-4-H), 8.49(1H,d, C-7-H), 9.83(1H, s, CHO)
2	4.3(3H, s, OCH_3), 7.27-7.31(1H, t, C-6-H), 7.41-7.47(1H, d, C-5-H), 7.42(1H,s, C-4-H), 8.38-8.40(1H, d, C-7-H)
3	4.70(2H, s, NH_2) 7.33-735(1H, t, C-6-H), 7.45-7.47(1H, d, C-5-H), 8.01(1H, s, C-4-H), 8.42-8.44(1H, d, C-7-H), 9.95(1H, s, NH)
4	7.29-7.31(1H, t, C-6-H), 7.46-7.48 (1H, d, C-5-H), 7.83(1H, s, C-4-H), 8.40-8.42(1H, d, C-7-H), 9.68 (1H, S, N-H)
5	7.25-7.32(5H, m,Ar-H), 7.58-7.60(1H, t, C-6-H), 7.84-7.85(1H, d, C-5-H), 7.94(1H, s, C-4-H), 8.59-8.61(1H, d, C-7-H), 8.84(1H, s, NH), 9.16(1H, s,NH), 10.56(1H, s, NH)
6	4.85(1H, s, NH), 7.21-7.31(5H, m, Ar-H), 7.30-7.33(1H, t, C-6-H), 7.44-7.46 (1H, d, C-5-H), 7.81(1H, s, C-4-H), 8.29-8.31(1H, d, C-7-H)

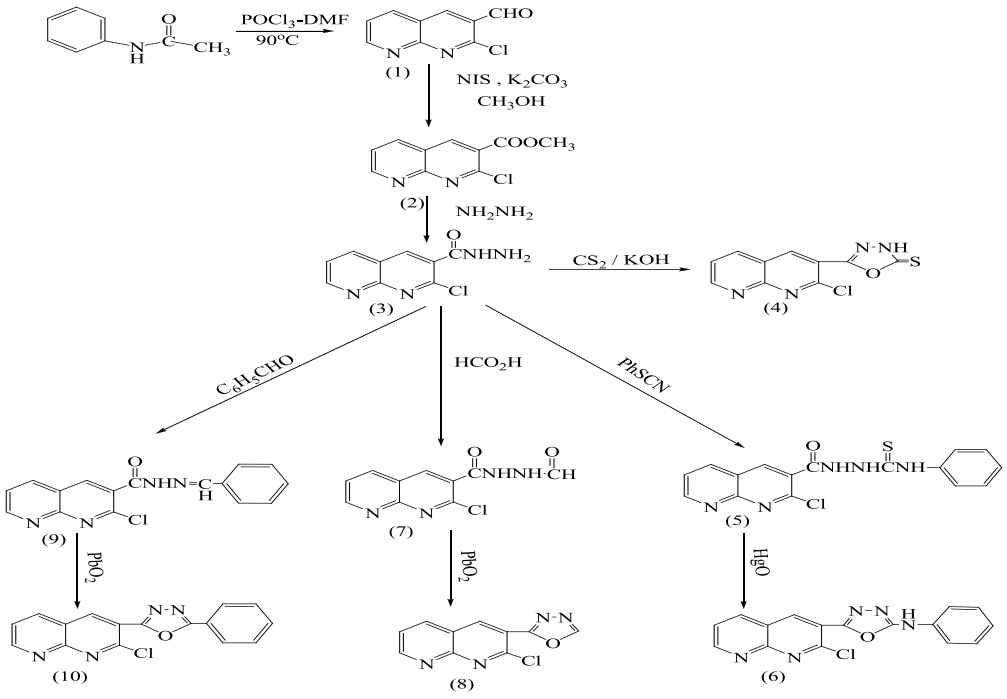
7	4.85(1H, s, NH), 7.12-7.21(5H, m, Ar-H), 7.30-7.33(1H, t, C-6-H), 7.44-7.46 (1H, d, C-5-H), 7.81(1H, s, C-4-H), 8.29-8.31(1H, d, C-7-H)
8	7.31-7.33(1H, t, C-6-H), 7.39-7.41 (1H, d-C-5-H), 7.81(1H,s, C-4-H), 7.95(1H, s, heterocyclic proton), 8.28-8.30(1H, d, C-7-H)
9	6.23-6.25(1H, m, =CH), 7.12-7.24(3H, m, Ar-H), 7.35-7.38(1H, t, C-6-H), 7.46-7.48(1H, d, C-5-H), 7.85(1H, s, C-4-H), 8.33-8.35(1H, d, C-7-H), 9.05(1H, s, NH)
10	711-723(5H, m, Ar-H), 7.31-7.33(1H, t, C-6-H), 7.49-7.51(1H, d,C-5-H), 7.86(1H, s, C-4-H), 8.42-8.44(1H, d, C-7-H)

BIOLOGICAL ACTIVE

The biological studies of compounds (4,6,8,10) were evaluated against *(Eschershia Coli, Proteus Vulgaris, Staphylococcus Epidermidis, Staphylococcus Areus)* table (3) the results showed that these compounds have a good activity against.

Table (3): Antibacterial activity data of compound (6-10,13-15)

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
4		18	22	13	10
6		23	21	16	11
8		18	19	14	15
10		15	14	15	14
Control	Ciprofloxacin 5mg/disk	-	-	15	14
	Chloramphenicol 30mg/disk	17	16	14	-



SCHEME-3-

CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of some new 1, 8-naphthyridine derivatives and characterized by spectral studies. The newly synthesized compounds (4,6,8,10) 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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