Synthesis of some heterocyclic derivatives of 1,8-Naphthyridine with a new substitution on the Naphthyridine ring

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Abstract

The Synthesis in good yields of some new 1,8-Naphthyridine derivatives (1-9) and characterized on the basis of IR and ^{1}H NMR spectra data. The compounds (1) and (6) were utilized as a starting material for the preparing of these compounds.

Keywords: 1,8- Naphthyridine , a new substitution, heterocyclic derivatives, Naphthyridine ring

Introduction:

1,8-Naphthyridine derivatives attracted considerable attention because 1,8-Naphthyridine skeleton is present in many compounds that have been isolated from natural substance with great importance due to their broad spectrum of biological activities. 1,8-Naphthyridine-3-carboxamide derivatives are used as anticancer and anti-inflammatory [1]. 1,8-Naphthyridine derivatives were found to display moderate cytotoxic activity against murine P338 Leukemia, when changes were carried out at N-1 and C-7 position [2,3], and [1,2,4]triazolo[4,3-a][1,8]Naphthyridine is displayed a fairly good anti-inflammatory activity; in addition, some derivatives showed very interesting analgesic properties [4]. Substituted 1,8-Naphthyridine compounds are used as antihypertensive, antiarrhythmic herbicide safeners and also as immunostimulants [5,6]. Indeed, some 5-(alkylamino)-N,N-diethyl[1,2,4]triazolo[4,3-a]-1,8-naphthyridine-6-carboxamide are used as anti-inflammatory [7-9].

Materails and Methods:

Instruments

Melting point were recorded on electrothermal CIA9300 melting point apparatus and are uncorrected, IR spectra were measured in KBr disks with a Buck 500 Scientific IR spectrophotometer. ^{1}H NMR spectrum was recorded by Bruker AM300 instrument using tetramethylsilane (TMS) as internal standard.

6-Nitro-2-morpholino-1,8-naphthyridine-4-carboxylic acid (1).

A solution of Morpholine-4-formyl (1.0mmol) and ethanol (10mL) as a solvent was heated in water bath at 30 °C and equimolar of 5-Nitro-2-aminopyridine (0.1399, 1.0mmol) in 10 mL of ethanol was added. The mixture was stirred and heated for (1 *hr*.) at 30 °C then pyruvic acid (1.0mmol) was added drop by drop with stirring and keeping the temperature below 50 °C for (1 *hr*.). The mixture was reflux for (24 *hr*.). Let the mixture at room temperature for (24 *hr*.). Distilled water (200mL) was added with stirring to the mixture. Brown precipitate was formed crystallized from ethanol. The melting point was (146-148 ºC) with 60% yield. The IR spectra and ^{1}H NMR of compound (1) are listed in table 1 and 2.

6-Nitro-2-morpholino-[4-*N*(diethylaminoethyl)]-1,8-naphthyridine (3).

In water bath, compound (1) (0.384gm, 1.0mmol) and an excess of thionyl chloride

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were refluxed for (2 *hr*.). The excess amount of thionyl chloride was removed under vacuum to give

6-Nitro-2-morpholino-1,8-naphthyridine-4-acidchloride (2). From a dropping funnel, toluene (20mL) was added drop wise to a mixture of compound (2) (0.322gm, 1.0mmol) and *N,N*-diethylethylenediamine* (1mmol). The reaction mixture was stirred at room temperature for (30 min.), refluxed for (2 *hr*.) and then neutralized with ice cold diluted HCl. The precipitate was filtered off, washed with cold water, dried, and crystallized from ethanol. The melting point was (186-188 ºC) with 55% yield. The IR spectra and ^{1}H NMR of compound (3) are listed in table 1 and 2.

***) N,N*-Diethylethylenediamine.**

In water bath, metoclopramide (3gm, 100mmol) and (10 mL) of 6N HCl were refluxed at (100 ºC) for (5 *hr*.). After cooling, the reaction mass was extracted three times with ether and the aqueous layer was collected and then evaporated under reduced pressure. The crude product was crystallized from ethanol-water mixture (7:3v/v). The melting point was (211-213 ºC) with 60% yield. The obtained hydrochloric salt of amine was dissolved in (30 mL) of distilled water and a sufficient amount of diluted sodium hydroxide added drop wise until the solution was alkaline to litmus. The miscible solution was concentrated and the pure amine was obtained by distillation at (146 ºC). The distilled light yellow liquid was used immediately.

6-Amino-2-morpholino-1,8-naphthyridine-4-carboxylic acid (4).

To warm solution of (0.52gm) of grease-free iron, (0.304gm, 0.02mol) of compound (1) and 2mL of concentrated HCl was added. The mixture was heated for (6 *hr*.) at 90 ºC. The mixture was cooled, filtered and washed with cold water, then recrystallized from a mixture of chloroform-ethanol (1:1v/v) to afford the compound (4). The melting point was (168-170 ºC) with 55% yield as a brown solid. The IR spectra and ^{1}H NMR of compound (4) are listed in table 1 and 2.

6-Acetylamino-2-morpholino-1,8-naphthyridine-4-carboxylic acid (5).

Acetic anhydride (0.5mL) was added to compound (4) (0.27gm, 1.0mmol) and the reaction was stirred overnight at 80 ºC. The excess acetic anhydride was removed under vacuum. Therefore, diethyl ether was added, and the solid separated was collected by filtration. The solid was washed thoroughly with $NaHCO_3$ solution, dried and crystallized from chloroform-ethanol to afford the compound (5). The melting point was (256-258 ºC) with 65% yield as a yellow-orange solid. The IR spectra and ^{1}H NMR of compound (5) are listed in table 1 and 2.

5-Chloro-2-morpholino-1,8-naphthyridine-4-carboxylic acid (6).

A solution of Morpholine-4-formyl (1mmol) and ethanol (10mL) as a solvent was heated in water bath at 30 °C and equimolar of 2-amino-4-chloropyridine (0.128 gm, 1.0mmol) in (10mL) ethanol was added. The mixture was stirred and heated for (1*hr*.) at (30 ºC). Then Pyruvic acid (1.0mmol) was added drop by drop with stirring and keeping the temperature below 50 ºC for (1*hr*.). The mixture was reflux for (24 *hr*.). Let the mixture at room temperature. Distilled water (200mL) was added with stirring to the solution. Brown precipitate was formed crystallized from chloroform-ethanol. The melting point was (141-143 ºC) with 65% yield. The IR spectra and ^{1}H NMR of compound (6) are listed in table 1 and 2.

5-Methoxy-2-morpholino-1,8-naphthyridine-4-carboxylic acid (7).

To methanolic solution of compound (6) (0.293gm, 1.0mmol), solid KOH (0.056 gm, 1.0mmol) was added and stirred for (4 *hr*.) at 90 ºC. The solvent was stripped off. The residue was added to water and extracted with chloroform. The solvent was evaporated to dryness to get the desired compound (7). The melting point was (165-167 ºC) with 70% yield. The IR spectra and ^{1}H NMR of compound (7) are listed in table 1 and 2.

5-Benzylamino-2-morpholino-1,8-naphthyridine-4-carboxylic acid (8).

A mixture of compound (6) (0.293gm, 1.0mmol) and distilled Benzylamine (0.5 mL) was heated for (6 *hr*.) at 120 ºC. The precipitate was washed with water followed by acetone and it was then air dried, the solid was crystallized from ethanol which afforded compound (8). The melting point was (256-258 ºC) with 35% yield. The IR spectra and ^{1}H NMR of compound (8) are listed in table 1 and 2.

1,2-bis[2-(2-morpholino-4-carboxy-1,8-naphthyridine-5-yloxy) ethoxyl]ethane (9).

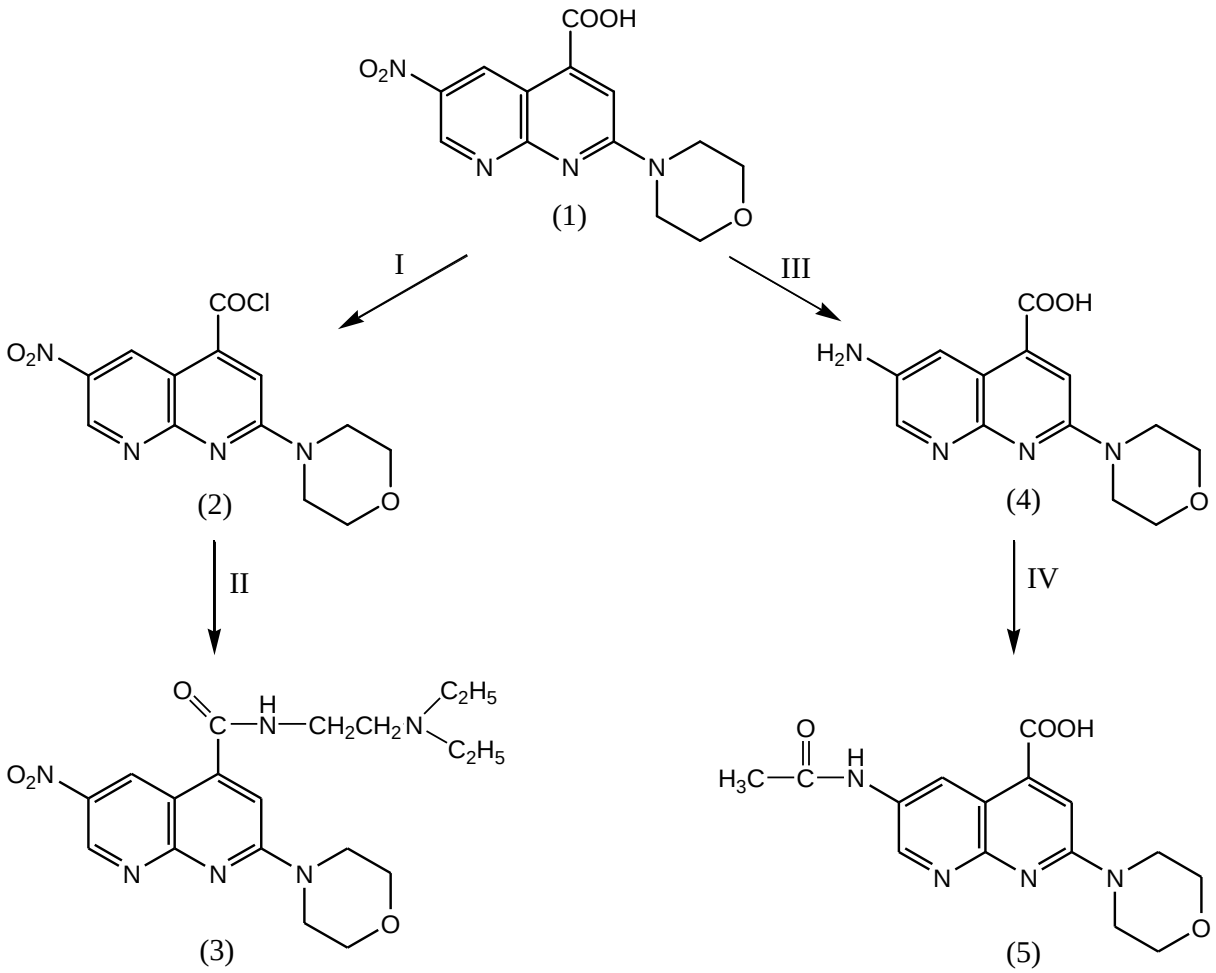
A solution of Triethyleneglycol (0.150gm, 1.0mmol) and KOH (0.112 gm, 2.0mmol) in dry THF (10mL) was added to solution of compound (6) (0.586gm, 2.0mmol) and the mixture was heated to 80 ºC for (24 *hr*.). Then the solvent was removed to dryness and dichloromethane was added to the residue. The organic layer was washed with water, dried (Na_2SO_3) and solvent was removed under reduced pressure to give orange precipitate. The melting point was (286-288 ºC) with 70% yield. The IR spectra and ^{1}H NMR of compound (9) are listed in table 1 and 2.

5-Amino-2-morpholino-1,8-naphthyridine-4-carboxylic acid (10).

To stirred solution of Sodium amide (0.433gm, 1.0mmol) in dry xylene (50mL), compound (6) was added and heated at 120 ºC under nitrogen for (12 *hr*.). The precipitate was filtered and poured on to ice to quench excess sodium amide. Water was removed by distillation under reduced pressure and the solid extracted with methanol-chloroform (3:7v/v) to afford the desired product (compound 10). The melting point was (215-218 ºC) with 30% yield. The IR spectra and ^{1}H NMR are listed in table 1 and 2.

Result and Discussion:

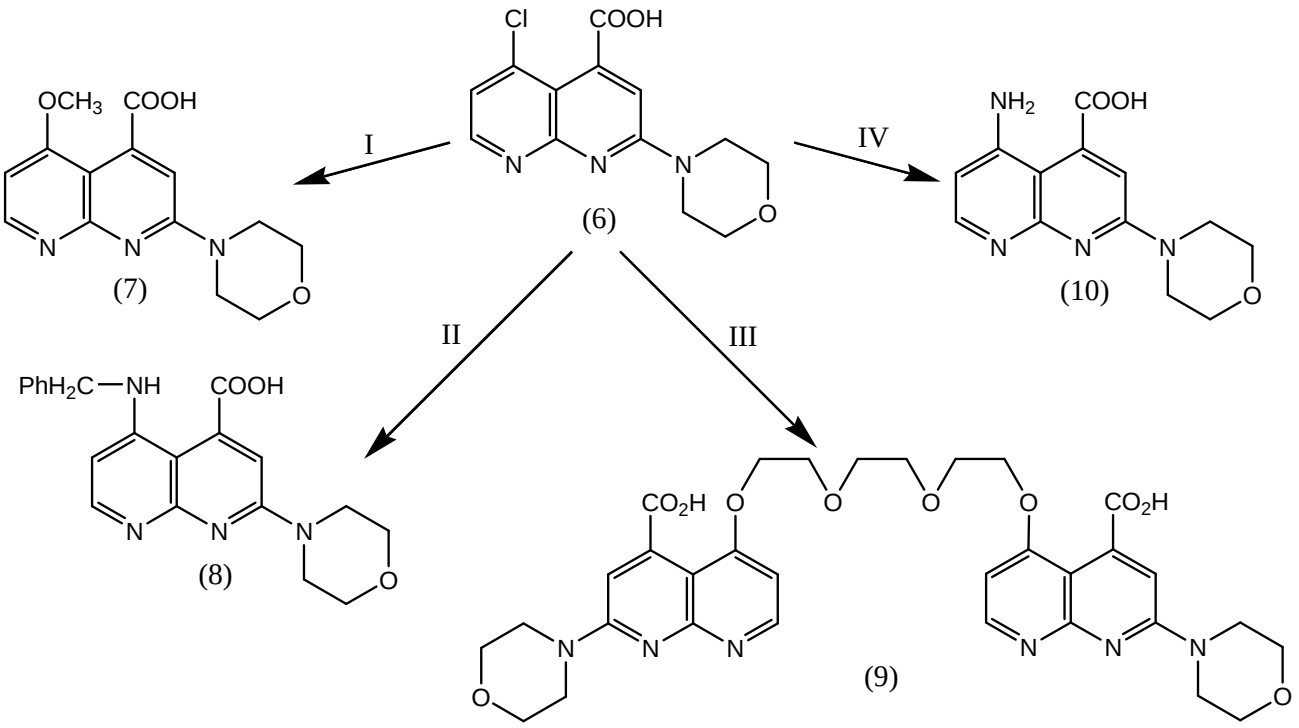
Naphthyridine (2-5) were synthesized starting from 6-Nitro-2-morpholino-1,8-naphthyridine -4-carboxylic acid (1) which was obtained from the condensation of 5-Nitro-2-amino pyridine, Morpholine-4-formyl and Pyruvic acid following a reported procedure [11]. The compound (1) is reduced with iron in acidic medium to the corresponding amine (4). The reaction of compound (4) and acetic anhydride lead to compound (5) with good yield. The reaction of compound (2) with *N*,*N*-diethylethylenediamine which is obtained from the hydrolysis of 4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxy benzamide (metoclopramide) in acidic medium afford compound (3). *Scheme (1)*:



Scheme (1)

Reagent and conditions:
(I) Thionyl chloride, 2 *hr*.
(II) Toluene, *N*,*N*-diethylethylenediamine, 2 *hr*.
(III) Water, Fe, HCl, 90 ºC, 6 *hr*.
(IV) Acetic anhydride, 80 ºC, 12 *hr*.

Compound (7) is made in good yield starting from 5-Chloro-2-morpholino-1,8-naphthyridine -4-carboxylic acid (6), which was obtained from condensation of 4-Chloro-2-aminopyridine, Morpholine-4-formyl and Pyruvic acid [11] by stirring at room temperature with methanolic hydroxide. The reaction of compound (6) with benzylamine lead to compound(8) in good yield while the reaction of compound (6) with Triethylene glycol lead to substitution of chlorine atom by hydroxyl function of Triethylene glycol. The compound (10) was synthesized in poor yield (30%) by refluxing compound (6) with $NaNH_2$ in xylene. *Scheme (2)*:



Scheme (2)

Reagent, conditions and yields:
(I) MeOH, KOH, 90 ºC, 70%.
(II) $PhCH_2NH_2$, 120 ºC, 35%.
(III) Triethylene glycol, KOH, THF, 80 ºC, 70%.
(IV) $NaNH_2$, 120 ºC, 30%.

Table (1): ^{1}H NMR data of compounds

Compound No.	^{1}H NMR (ppm) – DMSO-d_6
1	11.00 (s,1H), 8.45 (s,1H), 8.24 (s,1H), 8.11 (s,1H), 3.65 (t,4H), 2.88 (t,4H).
2	8.34 (s,1H), 8.20 (s,1H), 8.10 (s,1H), 3.65 (t,4H), 2.88 (t,4H).
3	8.68 (m,1H), 8.32 (s,1H), 8.20 (s,1H), 7.24 (bs,1H), 4.86-4.55 (m,4H), 3.68 (q,2H), 2.25 (t,3H), 3.95 (t,4H), 2.88 (t, 4H).
4	11.00 (s,1H), 8.38 (s,1H), 7.95 (s,1H), 7.85 (s,1H), 5.65 (bs,2H), 3.65 (t,4H), 2.94 (t,4H).
5	11.00 (s,1H), 8.45 (s,1H), 8.25 (bs,1H), 7.75-7.60 (m,1H), 7.32-7.20 (m,1H), 3.65 (t,4H), 2.85 (t,4H), 2.70 (s,3H).
6	11.00 (s,1H), 8.22 (s,1H), 7.86 (d,1H), 3.62 (t,4H), 2.86 (t,4H).
7	11.00 (s,1H), 8.66 (d,1H), 8.22 (d,1H), 7.95 (s,1H), 3.62 (t,4H), 2.86 (t,4H), 2.62 (s,3H).
8	11.00 (s,1H), 8.86 (d,1H), 8.44 (d,1H), 8.12 (s,1H),7.86 (bs,1H), 7.48-7.35 (m,5H), 4.55 (d,2H), 3.68 (t,4H), 2.84 (t,4H).
9	11.00 (s,1H),8.46-8.20 (m,1H), 7.95-7.68 (m,1H), 7.56-7.34 (m,1H), 4.62 (t,4H), 4.20 (t,4H), 3.96 (t,4H), 3.66 (t,4H), 2.82 (t,4H).
10	11.00 (s,1H), 7.85 (d,1H), 7.64 (d,1H), 7.15 (s,1H), 2.86 (t,2H), 3.62 (t,2H), 5.42 (bs,2H).

Table (2): Physical data of compounds

Comp. No.	Formula	m.p °C	Yield %	IR data							
				C=O	N – H	N – C	C=C, C=N	C-O-C	C – Cl	NO_2	OH
1	$C_{13}H_{12}N_4O_5$	146-148	60	1720	---	1420-1460	1580-1530	1180-1195	---	1475-1520	2900-3300
2	$C_{13}H_{11}N_4O_4Cl$	168-170	45	1775-1790	---	1420-1450	1580-1530	1180-1195	---	1480-1520	---
3	$C_{19}H_{26}N_6O_4$	186-188	55	1680-1640	3300-3250	1410-1450	1480-1580	1180-1195	---	1530-1450	---
4	$C_{13}H_{14}N_4O_3$	168-170	55	1775	3230-3150	1410-1450	1480-1580	1180-1195	---	---	2900-3150
5	$C_{15}H_{16}N_4O_4$	256-258	65	1730 and 1680-1640	3300-3175	1420-1460	1480-1580	1185-1195	---	---	2900-3250
6	$C_{13}H_{12}N_3O_3Cl$	141-143	65	1720	---	1415-1450	1480-1580	1190-1150	1125-1155	---	2900-3300
7	$C_{14}H_{15}N_3O_4$	165-167	70	1725	---	1415-1450	1480-1580	1190-1150	---	---	2900-3300
8	$C_{20}H_{20}N_4O_3$	256-258	35	1725	3250-3300	1410-1440	1480-1580	1175-1185	---	---	2900-3200
9	$C_{32}H_{36}N_6O_8$	286-288	70	1730	---	1415-1440	1480-1580	1190-1210	---	---	2900-3100
10	$C_{13}H_{14}N_4O_3$	215-218	30	1720	3150-3230	1420-1460	1470-1560	1185-1195	---	---	2900-3100

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تشييد لبعض المركبات الحلقيه غير المتجانسه المشتقه من 1.8 – نفثايردين بمعوضات على حلقة النفثايردين

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الخلاصة

حضرت مجموعة من مشتقات حوامض 8,1- نفثايريدين (1-9) وبنسب جيدة. شخصت المركبات المحضرة باستخدام الأشعة تحت الحمراء (IR) وطيف الرنين النووي المغناطيسي (^{1}H NMR)، حيث اعتبر المركبان (1) و (6) هما المادتان الأساسيتان لتحضير المركبات الأخرى.