Synthesis and Characterization of Some New Morpholine Derivatives

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Abstract:
In this paper a new series of morpholine derivatives was prepared by reacting the morpholine with ethyl chloro acetate in the presence triethylamine as a catalyst in benzene gave morpholin-N-ethyl acetate(1) which reacted with hydrazine hydrate in ethanol, and gave morpholin-N-ethyl aceto hydrizide (2) . Morpholin-N-aceto semithiocarbazide (3) were prepared by reacting compound(2) with ammonium thiocyanate , concentrated hydrochloric acid and ethanol as a solvent .Compound (3) reacted with sodium hydroxide and hydrochloric acid to give 5-(morpholin-N- methylene)-1H-1,2,4-triazole-3-thiol (4) .The new series of 1,2,4-triazol derivatives (5-8) was synthesized by reaction of compound(4) with formaldehyde , DMF as a solvent and different secondary amines. Preparation of new 1,2,4-triazoline derivatives (9) by reaction compound (4) with bromo acetic acid . Reaction of compound (9) with different aromatic aldehyde and dimethyl sulfoxide as a solvent obtained compounds (10-13).

Key words: Morpholine , 1,2,4-triazole and Mannich Reaction.

Introduction:
Morpholine is a six-membered heterocyclic compound [1]. It has synonyms Tetrahydro-1,4- oxazine; 1-Oxa-4-azacyclohexane; Diethylene oximide [2] and an organic chemical compound having the chemical formula O( CH₂CH₂)₂ NH , this heterocyclic structure features both amine and ether functional groups. As shown in the following Figure (1):

Fig.(1) Morpholine

Morpholine derivative plays an important role in the treatment of several diseases [3]. Morpholine derivatives find their wide spectrum of antimicrobial activity and insecticidal activity [4]. Morpholine used an emulsifier for cosmetics, rubless waxes,
Materials and Methods:
Chemicals used in this work are supplied from Merck, BDH, sigma Aldrich ND Fluka companies and are used without further purification. Melting points were recorded by using digital Stuart scientific SMP3 melting point apparatus and are uncorrected. FT-IR spectra were recorded on SHIMAZU FT-IR-8400 Fourier transform Infrared spectrophotometer using KBr discs in the (4000-6000) cm\(^{-1}\) spectral range. Internal reference measurements were made at College of Pharmacy- Al-Mustansiriya University. \(^1\)H-NMR and \(^13\)C-NMR spectra were recorded on Burker 500M Hz instrument using DMSO-d\(_6\) as solvent and TMS as internal reference measurements were made at the Chemistry Department, Al-Albyt University, Jordan.

Experimental:
Synthesis of Morpholin-N-ethyl acetate (1)\(^{18}\):
A mixture of morpholine (9 ml, 0.1mol), ethylchloro acetate(12ml, 0.1mol) and triethyl amine(10 ml, 0.1mol) with benzene as a solvent in (100ml) round bottom flask was refluxed for 6 h. at (115\(^\circ\)C). The resultant reaction mixture was cooled at room temperature and the solid was filtered, dried and recrystallized from ethanol. The physical properties of compound [1] are listed in Table (1).

Synthesis of Morpholin-N-acetoxydrazide (2)\(^{19}\):
A mixture of compound (1) (10ml, 0.05mol), hydrazine hydrate 80% (3ml, 0.05mol) and ethanol(20ml) were put in round bottom flask and refluxed for 6 h. The mixture was concentrated, cooled and the white crystal was filtered and recrystallized from ethanol. The physical properties of compound (2) are listed in Table (1).

Synthesis of Morpholin-N-acetosethio carbazide (3)\(^{20}\):
In (150ml) round bottom flask dissolved compound (2) and ammonium thiocyanate (5 gm, 0.06mol) in 10ml DMF then added 8ml HCL in absolute ethanol(50ml). The mixture was refluxed for 20h. The solvent was evaporated and the residue poured on crushed ice with stirring. The precipitate was filtered, dried and recrystallized from ethanol. The physical properties of compound (3) are listed in Table (1).

Synthesis of 5-(morpholin-N-methyl)-1H-1,2,4-Triazole-3-Thiol (4)\(^{21}\):
To a solution of compound (3)(2 gm, 0.01mol) in (5ml) DMF and (15ml) of 10% NaOH were refluxed for 3h. The mixture was treated with charcoal and then removed by hot filtration. The solution was acidified by 10%HCl with cooling. The precipitate was filtered, dried and recrystallized from ethanol. The physical properties of compound [4] are listed in Table (1).

General Methods for the Synthesis of 1,2,4-Triazoles(5-13)\(^{22}\):
A) Preparation of Morpholine Substituted 1,2,4-Triazoles (5-8):
In round bottom, flask was placed solution of compound (4) in 10 ml of DMF With (0.002 mol) of different amines (N-di-phenylamine, N-ethylaniline, N-diethylamine, N-di-n-butylamine) and formaldehyde (0.02 mol). The mixture was refluxed for 3h. The solvent was evaporated and the residue poured on crushed ice with stirring. The precipitate was filtered, dried and recrystallized from DMSO. The physical properties of compounds (5-8) are listed in Table (1).

B): Preparation of Morpholine Substituted 1,2,4-Triazoline (9-13):

In the round bottom, flask was dissolved (0.5 gm, 0.002 mol) of compound (19) and bromo acetic acid (0.3 gm, 0.002 mol) in 10 ml of DMSO then added triethyl amine (1 ml). The product was compound [9]. Then mixture was refluxed for 0.30 h. and added (0.002 mol) different aromatic aldehyde (benzaldehyde, 2,4-diethylamine benzaldehyde, m-nitrobenzaldehyde, p-hydroxybenzaldehyde) in presence 10% NaOH then refluxed for 1h. The solvent was evaporated and the residue was poured on crushed ice with stirring. The precipitate was filtered, dried and recrystallized from DMSO. The physical properties of compounds (9-13) are listed in Table (1).

Table (1): The Physical Properties of Prepared Compounds [1-13]

| Compd. No. | Nomenclature | Structure formula | Yield % | Color   | M. P. °C |
|------------|--------------|-------------------|---------|---------|----------|
| 1          | morpholin-N-ethyl acetate | ![Structure](image1) | 70      | Deep Brown | 232-233  |
| 2          | morpholin-N-acetohydrazide | ![Structure](image2) | 78      | White   | 105-106  |
| 3          | morpholin-N-aceto semithiocabazide | ![Structure](image3) | 88      | Light Yellow | 216-217 |
| 4          | 5-(morpholin methyl)-1H-1,2,4-triazole-3-thiol | ![Structure](image4) | 76      | Brown   | 221-222  |
| 5          | 5-(morpholin methyl)-3-thio(methyl-N-diphenyl amine)-1H-1,2,4-triazol | ![Structure](image5) | 62      | White   | 129-130  |
| 6          | 5-(morpholin methyl)-3-thio(methyl-N-ethyl phenylamine)-1H-1,2,4-triazol-3 | ![Structure](image6) | 55      | Light Brown | 127-128 |
Results and Discussion:
Preparation of Morpholin-N-ethylacetate (1):

The synthesis is sequences for preparation of series new morpholine derivatives by refluxing morpholine with ethyl chloro acetate in the presence of triethylamine and benzene as a solvent, as shown in the following equation:

\[
\text{morpholine} + \text{CHCl}_2\text{COOC}_2\text{H}_5 \xrightarrow{\text{Et}_3\text{N}, \text{reflux}} \text{morpholin-N-ethyldacetate} + \text{HCl}
\]

The FT-IR spectra as shown in Table (2) and Fig. (2) besides the \(^1\)H-NMR and \(^13\)C-NMR analysis of these compound (1) are listed in Table (3 and 4).

Synthesis of Morpholin-N-acetohydrazide (2):

Hydrazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds and play a very important role owing to their potentially high antifungal, antibacterial,
antiviral and antimalarial activity [24]. Hydrazide derivatives were prepared via treatment of prepared ester (1) with hydrazine hydrate in absolute ethanol, as shown in the following equation:

\[
\text{HOOC-CH}_3 + \text{HN-NH}_2 \xrightarrow{\text{ether}} \text{HOOC-CH}_3 \text{NH-NH}_2
\]

This reaction represents nucleophilic substitution reaction and its mechanism involved nucleophilic attack of amino group in hydrazine on carbonyl group in ester followed by elimination of ethanol molecule [25], as shown in the following Scheme:

The structure of the synthesized compound has been characterized and confirmed by FT-IR analysis as shown in Table (2).

**Synthesis of Morpholin-N-aceto thiosemicarbazide(3):**

The compound (2) was converted to thiosemicarbazide derivative compound (3) by the reaction with ammonium thiocyanate and hydrochloric acid in absolute ethanol as shown in the following equation:

\[
\text{HOOC-CH}_3 + \text{HN-NH}_2 + \text{SCN}^- + \text{H}^+ \xrightarrow{\text{ether}} \text{HN-C-CH}_3 \text{NH-NH}_2 \text{SCN}^-
\]

Mechanism of reaction involves nucleophilic attack of amino group of compound (2) on deficient carbon of ammonium thiocyanate followed by rearrangement of molecule [26] as shown in the following Scheme:

The FTIR spectra data showed in Table (2).

**Synthesis of 5-(morpholin methyl)-1H-1,2,4-Triazole-3-Thiol (4):**

The compound (3) was converted to compound (4) by reaction with1% NaOH in absolute ethanol and acidified by 10%HCl, as shown in the following equation:

\[
\text{HNHN-C-CH}_3 + \text{OH}^- \xrightarrow{\text{ether}} \text{HNHN-C-CH}_3 \text{SH} + \text{H}^+
\]

Mechanism of reaction involving nucleophilic attack lead to intramolecular cyclization [27,28] as shown in the following Scheme:

The FT-IR spectral data showed in Table (2).
Preparation of 5-[(Morpholin methyl)-3-thio(methyl-N-Substituted)-1H,2,4-Triazole (5-8):

A series of new Mannich derivatives was synthesized by the reaction between compound (4), secondary amine and formaldehyde, as shown in the following equation:

The mechanism of the reaction depends on the nucleophilis addition of amine to the carbon of formaldehyde followed by condensation with compound (4) gives the Mannich base [29,30], the suggested mechanism is shown in the following scheme:

The FT-IR spectra as shown in Table (2) and Fig. (3) beside the \(^1\)H-NMR and \(^{13}\)C-NMR analysis of these compounds (5-8) are listed in table (3 and 4) and Fig. [4,5].

Synthesis of 5-(Morpholin emethyl)-[2,3-b]-4-oxo-5-thiazolidenone-1H-1,2,4-Triazoline (9):

Treatment of compound (4) with bromo acetic acid in presence triethyl amine affords intramolecular cyclization to give compound (9), as shown in the following equation:

The mechanism of the reaction depends on the nucleophilic addition, as shown in the following mechanism [31]:

Synthesis of 5-(Morpholine methyl)-[2,3-b]-4-oxo-5-thiazolidine-1H-1,2,4-Triazoline (10-13):

Synthesis compounds (10-13) by reaction of compound (9) with different substituted aromatic aldehyde in presence 10% NaOH resulted the formation of aldol condensation of title compounds (10-13), as shown in the following equation:
The first step in condensation reaction, the hydroxyl ion abstract the proton from carbon adjacent the carbonyl to forms an enolate ion. The next step involved nucleophilic addition of enolate ion to another carbonyl group producing intermediate alkoxide ion. This alkoxide ion protonated to form aldol product and the last step form the $\alpha, \beta$-unsaturated products (10-13) [32], as shown in the following mechanism:

The FT-IR spectra as shown in Table (2) and Fig.(6) beside the ($^1$H-NMR and $^{13}$C-NMR) analysis of these compounds (5-8) are listed in Table (3 and 4). and Figure [7,8].

| Com. No. | $\nu$(C-H) cm$^{-1}$ Aromatic | $\nu$(C-H) cm$^{-1}$ Aliphatic | $\nu$(C=O) cm$^{-1}$amide | $\nu$(N-H) cm$^{-1}$ | $\nu$(C-O-C) cm$^{-1}$ | $\nu$(N-N) cm$^{-1}$ | Other Band cm$^{-1}$ |
|---------|-------------------------------|-------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| 1       | -                             | 2928                          | -                   | 1224                | -                   | -                   | $\nu$(C=O)ester 1743 |
| 2       | -                             | 2992                          | 1670                | 3100                | 1220               | 1496                | $\nu$(NH$_2$)3350, $\nu$(C-N) 1310                           |
| 3       | $^*$                          | 2999                          | 1650                | 3263                | 1124               | 1452                | $\nu$(NH$_3$) 3350, $\nu$(C-N) 1350, $\nu$(C=O) 1269, $\nu$(C=S)1315, $\nu$(C=O)1010 |
| 4       | $^*$                          | 2997                          | 1680                | 3269                | 1124               | 1464                | $\nu$(NH$_3$) 1610, $\nu$(C=O)1348, $\nu$(C=O) 1269, $\nu$(S=O)2682 |
| 5       | 3030                          | 2912                          | -                   | 1595-1516           | 3150               | 1165                | 1456-1419 $\nu$(C=O)1369, $\nu$(C=O)1058 |
| 6       | 3049                          | 2972                          | -                   | 1589                | 3132               | 1170                | 1448 $\nu$(C=O)1653, $\nu$(C=O)1332, $\nu$(C=O)752, $\nu$(C=O)1018 |
| 7       | $^*$                          | 2912                          | -                   | 3130                | 1172               | 1435                | $\nu$(C=O)1653, $\nu$(C=O)1371, $\nu$(C=O)734, $\nu$(C=O)1051 |
| 8       | $^*$                          | 2997                          | -                   | 3155                | 1201               | 1437                | $\nu$(C=O)1660, $\nu$(C=O)1311, $\nu$(C=O)698, $\nu$(C=O)1041 |
| 10      | 3003                          | 2916                          | -                   | 1527                | 3190               | 1199                | $\nu$(C=O)1651, $\nu$(C=O)1317, $\nu$(C=O)705, $\nu$(C=O)1022, $\nu$(C=O)1410 |
| 11      | 3001                          | 2910                          | -                   | 1530                | 3150               | 1231                | $\nu$(C=O)1693, $\nu$(C=O)1311, $\nu$(C=O)700, $\nu$(C=O)1066 |
| 12      | 3040                          | 2914                          | -                   | 1599                | 3160               | 1236                | $\nu$(C=O)1662, $\nu$(C=O)1336, $\nu$(C=O)727, $\nu$(C=O)1066 |
| 13      | 3015                          | 2935                          | -                   | 1550                | 3228               | 1130                | $\nu$(C=O)1747, $\nu$(C=O)1350, $\nu$(C=O)781, $\nu$(C=O)1031, $\nu$(OH)3477 |

Table (2): FTIR spectral data cm$^{-1}$ of the prepared compounds (1-13)
Table (3): $^1$H-NMR spectral Data (δ ppm) of Compounds [1,6,7,10,13]

| Com. NO | Compound Structure | $^1$H-NMR Spectral data (δ ppm) |
|---------|-------------------|---------------------------------|
| 1       | ![Structure1](image1) | δ2.5(s,2H,CH$_2$-N), δ3.4(s, 2H, CH$_2$-C=Oester) and δ3.7(s, 2H, CH$_2$-O) |
| 6       | ![Structure6](image6) | δ2.5(2H,CH$_2$-N), δ3.4(s,2H,CH$_2$-N), δ3.7(t,2H,CH$_2$-O), δ4.7(S,1H,N-CH$_2$-C, δ7.5(m,5H, CH aromatic), δ8.1(S,1H,NH) |
| 7       | ![Structure7](image7) | δ2.2(2H,CH$_2$-N), δ3.6(t,2H,CH$_2$-O), δ4.1(S,1H,N$_2$-CH$_2$-S), δ7.6(S,1H,CH=), δ8.2(m,5H,CH aromatic) |
| 10      | ![Structure10](image10) | δ2.1(S,IH,NH), δ2.3(S,2H,C-CH$_2$-N), δ2.5(t,2H,CH$_2$-N), δ3.6(t,2H,CH$_2$-O), δ4.1(S,1H,N$_2$-CH$_2$-S), δ7.6(S,1H,CH=), δ8.2(m,5H,CH aromatic) |
| 13      | ![Structure13](image13) | δ2(S,IH,NH), δ2.5(S,2H,C-CH$_2$-N), δ2.54(t,2H,CH$_2$-N), δ3.6(t,2H,CH$_2$-O), δ4.9(S,1H,N-CH$_2$-CH$_3$), δ7.6(S,1H,CH=), δ8.2(m,5H,CH aromatic) |

Table (3-7): $^{13}$C-NMR Spectral Data (δ ppm) of Compounds [1,6,7,10,13]

| Com. NO | Compound Structure | $^1$H-NMR Spectral data (δ ppm) |
|---------|-------------------|---------------------------------|
| 1       | ![Structure1](image1) | 14.1(CH3); 61.1(CH3CH2-O); 45(CH$_2$-N); 63(CH$_2$-O); 163(CH$_2$-C=O) |
| 6       | ![Structure6](image6) | 14(CH$_3$); 39(CH$_3$CH$_2$-N); 53(N-CH$_2$-C); 58(CH$_2$-N); 64(S-CH$_2$-N); 68(CH$_2$-O); 114-129 (6Caromatic); 161(CH=N) |
| 7       | ![Structure7](image7) | 10.8(CH$_3$); 39(N-CH$_2$-CH$_3$); 57(CH$_2$-N); 61(N-CH$_2$-S); 65(CH$_2$-O); 160(C=O) |
| 10      | ![Structure10](image10) | 45.5(CH$_3$-N); 59.43(N-CH$_2$-C); 61.1(CH$_3$-O); 90.19(S-CH$_2$-NN); 124(CH$_3$=); 128.52-129.17(6C aromatic); 164(N-C=O); 166(C=O) |
| 13      | ![Structure13](image13) | 55(CH$_2$-N); 66(CH$_2$-O); 88(S-CH-NN$^\prime$); 123.1(CH$_3$=); 129-144(CH aromatic); 166(CH-C-NN$^\prime$) |
Fig. (2): FT-IR spectrum for compound (1)

Fig. (3): FT-IR spectrum for compound (6)

Fig. (4): $^1$H-NMR spectrum for compound (6)
Fig. (5): $^{13}$C-NMR spectrum for compound (6)

Fig. (6): FT-IR spectrum for compound (10)

Fig. (7): $^1$H-NMR spectrum for compound (10)

Fig. (8): $^{13}$C-NMR spectrum for compound (10)
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تحضير وتستخيص بعض المشتقات الجديدة للمورفولين

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الخلاصة:

في هذا البحث تم تحضير سلسلة جديدة من مشتقات المورفولين المحضرة من خلال تصعيد المورفولين مع كلوريد خلات الأيثيل وثلاثي الأيثيل امين كعامل مساعد في البنزين حيث تم الحصول على المركب مورفولين -N- خلات الأيثيل (1) وتفاعلاته مع الهيدرازين في الايثانول أعطى مورفولين-N-خلات الهيدرازين (2) الذي أعطي مورفولين-N-خلات سيمي ثابي كاربازايد(3) من تفاعل المركب (2) مع امونتيلوسياتانيد وحمض الهيدروكلوريك المركز والائيتانول كمنب تفاعل المركب(3) مع هيدروكسيد الصوديوم وحمض الهيدروكلوريك ليعطي 5-(مورفولين-N-ميثيل) -1,2,4,2,1-ترايازول-3-ثنائي(4). سلسلة جديدة من مشتقات 1,4,2,3-ترايازول (5-8) من تفاعل مركب (4) مع الفورمالدهيد وثنائي ميثيل فورم امايد كمنب مع مجموعة من الأمينات الثانوية حضرت مشتق واحد (9) من 4,2,2-ترايازولين من خلال تفاعل المركب (4) مع برومو حامض الخليك. تم مفاعلة المركب (9) مع الديكسيكيد اروماتية مختلفة يوجد ثنائي ميثيل سلفوكسايد كمنب لتحضير سلسلة من مركبات (10-13). حيث تم تشيخص هذه المشتقات بواسطة درجات FT-IR 13C-NMR 1H-NMR and.

الكلمات المفتاحية: مورفولين، 4,2,2-ترايازول، تفاعلات مانخ

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