

## Synthesis of some Heterocyclic Compounds from 1,4-Benzoxazine-3-one

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### الخلاصة

المركب (1) المحضر من تفاعل 2-امينو فينول مع برومو خلات الاثيل، ومعاملة برومو خلات الاثيل مع المركب (1) ليعطي المركب (2)، بينما المركب (3) ينتج من تفاعل الهيدرازين المائي مع المركب (2). المركب (3) استخدم كنواة لتحضير المركبات (4-12) بتفاعله مع مختلف الكواشف الكيميائية. تفاعل (11) مع ثايوكلايكولك اسيد، 3-كلورو حامض البنزويك الفوقي ليعطي (13، 14) على التوالي، بينما المركب (15) المحضر من تفاعل (12) مع كلورو اسيتايل كلورايد. النتائج شخست فيزيائيا وكيميائيا وبالطرائق الطيفية.

### Abstract

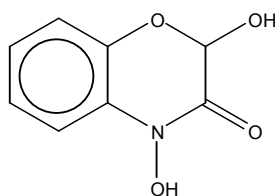
The compound (1) was synthesized by reacting 2-amino phenol with ethyl bromo acetate. The treatment of ethyl bromo acetate with compound (1) gave (2), While compound (3) was produced by reacting hydrazine hydrate with compound (2). Compound (3) was used as precursor to prepare (4-12) by reacting it with different chemical reagents. The reaction of (11) with thioglycolic acid, 3-chloro perbenzoic acid afforded (13,14) respectively, while compound (15) was prepared from the reaction of (12) with chloro acetyl chloride. The products were identified by physical, chemical and spectroscopic methods.

### Introduction

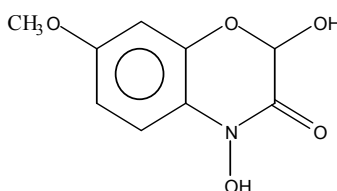
Derivatives of 2,3-dihydro-3-oxo-1,4-benzoxazine are well known<sup>(1)</sup>. these nitrogen-oxygen containing heterocyclic compounds were prepared by heating  $\alpha$ -halogenacyl-o-anisidides with aluminum chloride as catalyst<sup>(2)</sup>. Versatile methods were used for the preparation of these compounds using o-amino phenoxy acetic acid in presence of platinum oxide or o-chloro acetamido phenol in weakly alkaline solution<sup>(1,3)</sup>.

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Various benzoxazine derivatives have been shown to have interesting pharmacological properties<sup>(4)</sup>. A group of 1,4-benzoxazine-3-one was isolated from maize, wheat and rye<sup>(5)</sup>, therefore 2H-1,4-benzoxazine-3-(4H)one was used as heterocyclic scaffolds for design of cardiovascular, anti psychotic, anti depressive and anti bacterial drugs<sup>(6,7)</sup>, like 2,4-dihydroxy-(2H)-1,4-benzoxazine-3-(4H) one



and 2,4-dihydroxy-7-methoxy(2H)-1,4-benzoxazine-3-(4H) one



Interesting bioactivity was observed for both compounds, some of their degraded products, and also some synthetic analogues shows antimicrobial, antifeedant, insecticidal<sup>(8)</sup>, and were found to inhibit germination of spores of the phytopathogenic fung<sup>(5)</sup>. N-alkylation of 2H-1,4-benzoxazine-3-one was performed to prepare N-ester, and hydrazide compounds by treatment with ethyl bromo acetate in presence of anhydrous potassium carbonate<sup>(9)</sup>, The above compound was also used to prepare hydrazide compound by the treatment of this compound with hydrazine hydrate<sup>(10)</sup>. Preparation of Some heterocyclic compounds by the treatment of hydrazide derivative with different chemical reagent. As mentioned heterocyclic compounds were prepared from hydrazide derivatives may be beneficial as bioactivities.

### Experimental

1. Melting points were determined by Electro thermal IA 9000.
2. Infra red spectrophotometer Model Tanser 27 Bruker Co. Germany was used to measure the IR spectra.

#### 2H-1,4-benzoxazine-3-one (1)<sup>(11)</sup>

A mixture of (0.01 mole) 2-amino phenol and (0.01 mole, 0.23 g) sodium metal dissolved in 25 ml absolute ethanol was refluxed for 15 min. and then added (0.01 mole) ethyl bromo acetate then refluxed for 15 hrs, The solvent was evaporated under reduced pressure and poured into crushed ice, the precipitate was separated by filtration, washed with water, dried and recrystallized from ether to obtain red compound (1.3 g, 87%), m.p 170-171 C°. This compound was prepared as mentioned in literature<sup>1</sup> m.p(171-172C°).

**Ethyl-(1,4-benzoxazine-3-one-4-yl)-acetate (2)**<sup>(12)</sup>

A mixture of a compound (1) (0.01 mole), ethyl bromo acetate (0.01 mole) and potassium carbonate anhydrous (2 g) in 50 ml dry acetone was refluxed for 15 hrs, The solvent was evaporated under reduced pressure, poured into crushed ice, the precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain red compound (1.6 g, 68%), m.p (69-71 C°).

**2H-1,4-benzoxazine-3-one-4-yl-acetic acid hydrazide (3)**<sup>(12)</sup>

A mixture of compound (2) (0.0125 mole) and hydrazine hydrate 80% (0.06250mole) in absolute ethanol 100ml was refluxed for 10 hrs, The solvent was evaporated under reduced pressure, poured into crushed ice, the precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain white compound (1 g, 72%), m.p (162-164 C°).

**5-[(2H-1,4-benzoxazine-3-one-4-yl)-methyl]-1,3,4-oxadiazole-2-thiol(4)**<sup>(13)</sup>

A mixture of compound (3) (0.0025 mole), potassium hydroxide (0.0025 mole) in 25 ml absolute ethanol and then added to it carbondisulphide (0.0025 mole, 0.15 ml) was refluxed for 6 hrs, poured into crushed ice followed by adding drops of dilute hydrochloric acid with stirring, the precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain brown compound (0.36 g, 54%), m.p (194-196 C°).

**6-[(2H-1,4-benzoxazine-3-one-4-yl)-methyl]-1,2,3-trihydro-4-oxo-1,2,5-triazine (5)**<sup>(14)</sup>

A mixture of compound (3) (0.002 mole),  $\alpha$ -chloro acetamide (0.002 mole) in 30 ml N,N-dimethyl formamide (DMF) was refluxed for 25 hrs, The solvent was evaporated under reduced pressure and then poured into crushed ice, The precipitate was separated by filtration, washed with water, dried and recrystallized from tetrahydro furan (THF) to obtain red compound (0.36 g, 69%), m.p (218-220 C°).

**6-[(2H-1,4-benzoxazine-3-one-4-yl)-methyl]-2,3-dihydro-4-oxo-5-oxapyridazine (6)**<sup>(15)</sup>

A mixture of compound (3) (0.002 mole), chloro acetic acid (0.002 mole), sodium acetate (0.002 mole) in 25 ml acetic anhydride was refluxed for 7 hrs, poured into crushed ice, The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain white compound (0.32 g, 61%), m.p (141-143 C°).

**N-[(2-H-1,4-benzoxazine-3-one-4-yl)-acetamido]- phthalimide (7)**<sup>(16)</sup>

A mixture of compound (3) (0.002 mole), phthalic anhydride 90.002 mole) in 30 ml glacial acetic acid was refluxed for 6 hrs and then

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poured into crushed ice, the precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain white compound (0.5 g, 71%), m.p (220-222 C°).

### N-[(2-H-1,4-benzoxazine-3-one-4-yl)-acetamido]-2,5-dimethyl pyrrole (8) <sup>(15)</sup>

A mixture of compound (3) (0.002 mole), acetyl acetone (0.002 mole) in 30 ml glacial acetic acid was refluxed for 8 hrs and then poured into crushed ice. The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain brown compound (0.5 g, 83%), m.p (201-203 C°).

### 5-(2H-1,4-benzoxazine-3-one-4-yl)-1,2,5-trihydro-3,4,6-tri-oxo-pyridazine (9) <sup>(17)</sup>

A mixture of compound (3) (0.01 mole), diethyl oxalate (0.01 mole), sodium metal (0.23 g) in 30 ml absolute ethanol was refluxed for 12 hrs. After the mixture was cooled a drops of dilute hydrochloric acid were added, The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain pure brown compound (2.1 g, 76%), m.p (150-151 C°).

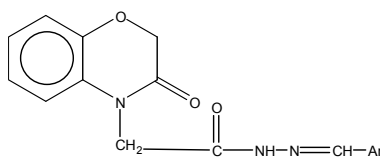
### 5-(2H-1,4-benzoxazine-3-one-4-yl)-1,4,5-trihydro-6-oxo-pyridazine(10) <sup>(17)</sup>

A mixture of compound (3) (0.01 mole), chloro acetaldehyde diethyl acetyl (0.01 mole), sodium metal (0.23 g) in 40 ml absolute ethanol was refluxed for 20 hrs and then to the cold mixture drops of dilute hydrochloric acid were added, The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain a brown compound (1.8 g, 73%), m.p (146-147 C°).

### Hydrazone compounds (11,12) <sup>(18)</sup>

A mixture of compound (3) (0.00125 mole), aromatic aldehyde (0.00125 mole) in 30 ml absolute ethanol was refluxed for 5 hrs, cooled. The precipitate was separated by filtration, dried and recrystallized from ethanol to obtain compounds, as shown in table (1)

Table (1): some physical properties of hydrazones



Comp. No	Ar	colour	m.p C°	% yield
11	p-(CH <sub>3</sub> ) <sub>2</sub> -N-C <sub>6</sub> H <sub>5</sub>	White	245-246	90
12	m-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	White	276-278	90

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**3-[(2H-1,4-benzoxazine-3-one-4-yl)-acetamido]-2-[4-(N,N-dimethyl amino) phenyl]-4-oxo-1,3-thiazolidine (13)** <sup>(18)</sup>

A mixture of hydrazone (11) (0.005 mole) and thio glycolic acid (0.006 mole) in dry benzene was refluxed for 24 hrs, the solvent was evaporated under reduced pressure, a solution of dilute sodium bicarbonate was then added. The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain brown compound (1.76 g, 82%), m.p (227-229 C°).

**2-[(2H-1,4-benzoxazine-3-one-4-yl)-acetamido]-3-[4-(N,N-dimethyl amino) phenyl]-oxaziridine (14)** <sup>(19)</sup>

A solution of 3-chloro perbenzoic acid (0.001 mole) was added drop wise with stirring in 2.5 ml dry pyridine to a solution of hydrazone compound (11) (0.001 mole) in 5 ml dry pyridine, the mixture was stirred for 6 hrs and then poured into crushed ice. The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain brown compound (0.2 g, 54%), m.p (226-228 C°).

**1-[(2H-1,4-benzoxazine-3-one-4-yl)-acetamido]4-[4(N,N-dimethyl amino) phenyl]-3-chloro-2-oxo- azetidine (15)** <sup>(20)</sup>

A mixture of hydrazone compound (12) (0.005 mole), triethyl amine (0.01 mole) in 30 ml dry 1,4- dioxane, chloro acetyl chloride (0.01 mole) was added drop wise with stirring for 30 min. at room temperature. The mixture was refluxed for 3 hrs, the solvent was evaporated by reduced pressure and poured into crushed ice, then the precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol to obtain brown compound (1.9 g, 88%), m.p (282-283 C°).

## Results and discussion

The parent compound (1) was prepared by reaction of ethyl bromo acetate with 2-amino phenol in presence of sodium ethoxide.

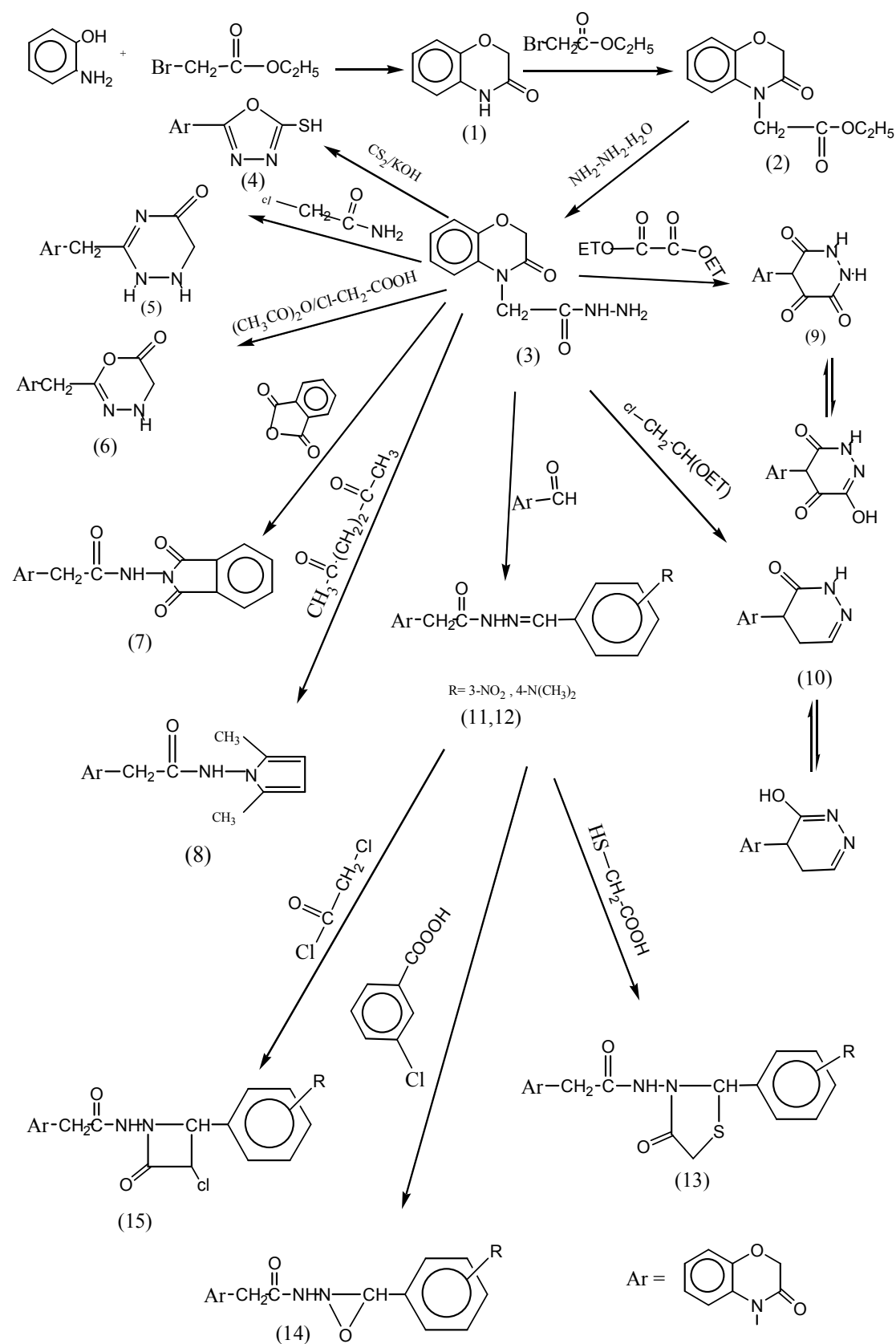
The ester compound (2) was prepared by reacting of compound (1) with ethyl bromo acetate in presence of potassium carbonate.

The ester compound (2) was identified by the appearance of the following band at (1739 cm<sup>-1</sup>) for the ester carbonyl band, carbonyl of amide at (1680 cm<sup>-1</sup>) and disappearance of N-H stretching for amide, (2914 cm<sup>-1</sup>) for C-H stretching and (1280 cm<sup>-1</sup>, 1090 cm<sup>-1</sup>) for C-N band and appear C-H band for CH<sub>3</sub> at (1377 cm<sup>-1</sup>).

The ester compound (2) was reacted with excess amount of hydrazine hydrate to produce hydrazide compound (3), the hydrazide compound was identified by disappearance of ester carbonyl band and the appearance of the following bands (1688 cm<sup>-1</sup>, 1671 cm<sup>-1</sup>) for amide carbonyl of lactone & hydrazide respectively, (1284 cm<sup>-1</sup>) for C-N, C-H band was shown at (2852 cm<sup>-1</sup>) and another band at (3334 cm<sup>-1</sup>) for N-H stretching.

compound (3) was used to prepare a number of heterocyclic compounds as indicated in scheme (1).

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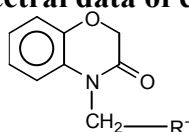


Scheme (1): Synthesis of some heterocyclic derivatives from 1,4-benzoxazine-3-one

The compounds (4-6) were synthesized by the reaction of hydrazide (3) with carbon disulphide in ethanolic solvent,  $\alpha$ -chloro acetamide in presence of triethylamine or  $\alpha$ -chloro acetic acid in presence of sodium acetate and acetic acid to produce compounds 4,5,6 respectively.

The structures of these compounds were confirmed by (IR spectra) Table (2). The significant absorption peaked at  $(3135-3436)\text{cm}^{-1}$  due to N-H stretching, carbonyl amide appear at  $(1649-1682)\text{cm}^{-1}$  and carbonyl ester for compound (6) was absorbed at  $(1744\text{ cm}^{-1})$ , C-O sym and asy bands at  $(1088-1163)\text{cm}^{-1}$ ,  $(1219-1240)\text{cm}^{-1}$  respectively and the C-H stretching at  $(2924-2936)\text{cm}^{-1}$ , C=N stretching absorption at  $(1595-1657)\text{cm}^{-1}$  while C=S band for compound (4) at  $1197\text{cm}^{-1}$ .

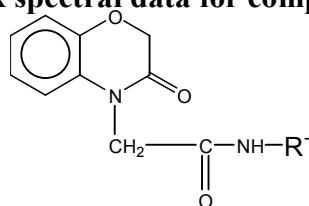
**Table (2): IR spectral data of compounds (4- 6).**



Comp. No	R'	IR (KBr) $\text{vcm}^{-1}$						
		N-H	C=O amide	C=O lactone	C=S	C-O Sy asy	C=N	C-H
4		3135	1649		1197	1163 1240	1595	2948
5		33313	1682				1657	2924
6		3436	1681	1744		1088 1219	1608	2963

The structures of compounds (7,8) showed significant absorption peaked at  $(3222 -3278)\text{cm}^{-1}$  for N-H stretching and there were two bands appeared at  $(1747\text{ cm}^{-1})$ ,  $(1697\text{ cm}^{-1})$  due to phthalimide moiety and carbonyl of the amide appear at  $(1684-1685)\text{cm}^{-1}$  and C=C band appeared at  $1684\text{ cm}^{-1}$  for compound (8) and C-H bands at  $(2960-2983)\text{cm}^{-1}$ .

**Table(3): IR spectral data for compounds (7, 8)**

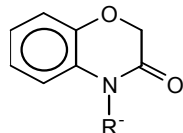


Comp. No	R'	IR (KBr) $\text{vcm}^{-1}$					
		N-H	C=O phthalimide	C=O amide	C=C	C-H	CH <sub>3</sub>
7		3222	1747 1697	1685		2960	
8				1684	1684	2983	1404

The infrared of compounds (9,10) show a peak at  $(3177-3196)\text{cm}^{-1}$  for N-H stretching and bands of amide carbonyl band at  $(1684-1686)\text{cm}^{-1}$

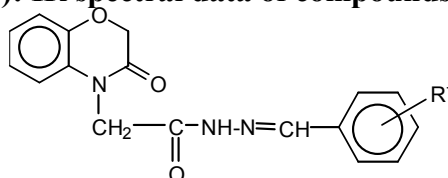
while a band appeared at  $1655\text{ cm}^{-1}$  related to C=O group of compound (9) while further bands appeared at  $3447\text{ cm}^{-1}$ ,  $2926\text{ cm}^{-1}$  for O-H, C-H respectively and the C=N band for compounds (9,10) appeared at  $1655\text{ cm}^{-1}$ .

**Table (4): IR spectral data of compounds (9, 10)**



Comp.No	R	IR (KBr) $\text{vcm}^{-1}$					
		N-H	C=O amide	C=O ketone	O-H	C-H	C=N
9		3177	1655	1684	3447	2926	
10		3196	1686		3447	2926	1655

**Table (5): IR spectral data of compounds (11, 12).**



Comp.No	R	IR (KBr) $\text{vcm}^{-1}$					
		N-H	C=O	C=N	N=O Sym asy	C-H	CH <sub>3</sub>
11	-4-N(CH <sub>3</sub> ) <sub>2</sub>	3452	1677	1606		2900	1361
12	-3-NO <sub>2</sub>	3442	1699	1666	1352 1530	2949	

The structure of compounds (11,12) were confirmed from IR data as shown in Table (5). The IR showed absorption band at  $(3442-3452)\text{ cm}^{-1}$  which was attributed to the stretching of N-H, while the bands in range  $(1677-1699)\text{ cm}^{-1}$  related to the stretching vibration of amide carbonyl, C=N bands appeared at  $(1606-1666)\text{ cm}^{-1}$ , N=O band sym, asy appeared at  $(1352\text{ cm}^{-1}, 1530\text{ cm}^{-1})$  respectively, C-H band at  $(2900\text{ cm}^{-1}-2949\text{ cm}^{-1})$ .

While compound (13) was synthesized by the reaction of compound (12) with thioglycolic acid to give compound (13).

The IR spectra of compound (13) showed significant absorption bands at  $1738\text{ cm}^{-1}$  which due to stretching vibration of amide carbonyl while the band at  $3446\text{ cm}^{-1}$  for N-H while C-H band appeared at  $2923\text{ cm}^{-1}$  and C-S band appeared at  $747\text{ cm}^{-1}$ .

Compound (14) was synthesized by the reaction of compound (11) with oxidizing reagent 3-chloro per benzoic acid to give compound (14).

The structure of compound (14) was identified by the following significant absorption bands at  $3214\text{ cm}^{-1}$  for N-H stretching, amide carbonyl at  $1674\text{ cm}^{-1}$  and C-O at  $1055\text{ cm}^{-1}$  and N-O band at  $816\text{ cm}^{-1}$ , C-H band at  $2900\text{ cm}^{-1}$ .



Compound (15) was synthesized by the reaction of compound (12) with chloro acetyl chloride to give compound (15).

The structure of this compound was identified by IR spectroscopic data shown in the significant absorption peak at  $3187\text{ cm}^{-1}$  due to N-H stretching and the carbonyl of the new ring appeared at  $1739\text{ cm}^{-1}$ , carbonyl of the amide appeared at  $1699\text{ cm}^{-1}$ , while N=O band sym, asy absorbed at  $1353\text{ cm}^{-1}$ ,  $1531\text{ cm}^{-1}$  respectively, C-H band at  $2948\text{ cm}^{-1}$  and C-Cl band at  $699\text{ cm}^{-1}$ .

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