Synthesis of some Novel Pyrazolo and Triazolo Quinolines from Coumarin Compounds

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ABSTRACT

Coumarin and its furo derivatives (psoralene and isopsoralene) are used as precursor for preparation of heterocyclic compounds. The 4-methyl-7-mthoxycoumarin, psoralene and substituted isopsoralene (II, III and IV) which are derived from 4-methyl-7-hydroxycoumarin (I), when reacted with hydrazine hydrate through nucleophilic substitution reaction under basic condition give N-amino-2-quinolone and its furo derivatives (1,5 and 9) in good yields.

Reaction of these compounds (1,5 and 9) with methyl acetoacetate, ethyl acetoimidate or thiosemicarbazide, a new heterocyclic compounds will be formed pyrazolo-quinoline and it is furo derivatives (2,6 and 10); 1,2,4-triazolo-quinoline and its furo derivatives (3,7 and 11) and 1,2,4-triazolo-quinoline-2-thione (4,8 and 12) respectively.

The assigned structure of the prepared compounds were elucidated by the available physical and spectral methods IR, UV and \textsuperscript{1}H-NMR.

Keywords: coumarin derivative, N-amino-2-quinolone, pyrazolo and triazolo quinoline.
INTRODUCTION

The formation of fused heterocyclic rings is an important task for heterocyclic chemists from various points of view.

Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. A review article dealing with the varied physiological activities of coumarin derivatives has been published describing their anticoagulant properties (Arora et al., 1963; Dirk et al., 2011; Ghulam et al., 2007), antibacterial (Ramachandra et al., 2010), antifungal (Soroush et al., 1999), anti-inflammatory (Borges et al., 2005) and antitumor activities (Manfredini et al., 1997).

The nucleophilic substitution reaction of coumarin with ammonia derivatives (amine, hydrazine, phenyl hydrazine, … etc.) proceed through ring opening of the pyrone ring and recyclized to form N-substituted-2-quinolone derivatives (Katritzky et al., 1984). The reaction of coumarin with hydrazin hydrate in the presence of pyridine gives N-amino-2-quinolone and its derivatives (Al-Bayati et al., 2010).

The quinolone derivatives are important due to their biological and pharmaceutical activities such as antitumor (Joseph et al., 2002), antimalarial (Xiao et al., 2001), antiplatelet (Nishi et al., 2000), antidepressant (Oshiro et al., 2000), antiulcer (Banno et al., 1988), antioxidant agent (Al-Omer et al., 2006) and herbicide activities (Khan et al., 2003). Also anumber of quinolone compounds are important as synthone in organic synthesis (Godard et al., 1994).

Pyrazole and triazole derivatives are also important due to their biological activities (Michael et al., 1996), antimycotic (Liming et al., 2006) and widely used in both human and veterinary therapy and as agricultural fungicides and human fungal disease (Menegola et al., 2001).

In this presentation, a series of new heterocyclic compounds pyrazole and triazole were prepared from coumarin and it is furo derivatives. The furo coumarin compounds (III and IV) are prepared as in the published research (Traven et al., 2003; Adriana et al., 2002) by starting from 4-methyl-7-hydroxycoumarin (I) which is alkylated with allyl bromide, the obtained ether were subjected to a Claisen rearrangement followed by cyclization of the rearrangement product in the presence of acid.

EXPERIMENTAL

Melting points were measured on electrothermal Gallen Kamp melting points apparatus and uncorrected. Infrared (FT.IR.) spectra were recorded as (KBr) disk using a Brucker FT.IR.
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spectrophotometer 2003. Ultraviolet (UV) spectra were performed on Shimadzu UV-Visible spectrophotometer, UV-1650. \textsuperscript{1}H-NMR were recorded by Brucker (300MHz) in Jordan.

**Synthesis of N-amino-2-quinolone and it is furo derivatives (1,5 and 9) (Vinoda et al., 2004).**

To a mixture of (1 mmole) of coumarin compounds (II, III and IV) in (10 ml) pyridine, hydrazine hydrate (95 \%) (10 ml) was added drop wise with stirring at room temperature. The mixture was refluxed for (2 hrs), then cooled, and the solid product was filtered off, washed with water then recrystallized from ethanol. The physical and spectral data were shown in Table (1).

**Synthesis of pyrazoloquinoline and it is furo derivatives (2,6 and 10) (Shelton et al., 2003).**

In the first step:

A mixture of (1 mmole) of N-amino-2-quinolone (1,5 and 9), methyl acetoacetate (10 mmole) and few drops of p-toluene sulphonic acid was stirred for (4 hrs) at 130 \(^\circ\)C then cooled and the solid product was collected by filtration, washed with water and recrystallized from ethanol.

In the second step: the product from the first step (1 mmole) was dissolved in (10 ml) DMF then sodium acetate (0.1 mmole) was added. The mixture was refluxed for (1 h), cooled and the solid product was collected by filtration, washed with water and recrystallized from ethanol. The physical and spectral data were shown in Table (1).

**Synthesis of triazoloquinoline and it is furo derivatives (3,7 and 11) (Konda et al., 2010; Abd-El-Fatah et al., 2010).**

Ethyl acetimidate (1 mmole) [which prepared according to the published procedure (Vogel, 2007)] was added to a mixture of (30 ml) 10 \% sodium carbonate solution and (30 ml) toluene to form two layers. The mixture was shaken then the organic layer was separated. To the organic layer N-amino-2-quinolone (1, 5 and 9) (1mmole) was added, then refluxed for (3 hrs), cooled and the solid product was filtered, washed with water and recrystallized from ethanol. The physical and spectral data were shown in Table (1).

**Synthesis of triazoloquinoline-2-thione and it is furo derivatives (4,8 and 12) (Hussain et al., 1997).**

A mixture of coumarin compounds or it is furo derivatives (II, III and IV) (1 mmole) and thiosemicarbazide (1 mmole) in DMF (20 ml). was refluxed for (3 hrs). The reaction mixture was cooled and the solid product was filtered off, washed with water and recrystallized from ethanol. The physical and spectral data were shown in Table (1).

### RESULTS AND DISCUSSION

The synthetic pathway leading to the title compounds is given in scheme (1). The key intermediate N-amino-2-quinolone and it is furo derivatives (1, 5 and 9) could be prepared by the reaction of coumarin derivatives with hydrazine hydrate through ring opening of pyrone ring then recylcized to form N-amino-2-quinolone derivatives as in (eq. 1) (Youssef et al., 2006).
The proposed mechanism for this reaction is nucleophilic substitution through the attacking the carbonyl carbon atom by the unshared pair of electrons of nitrogen atom in hydrazine hydrate. This step is accompanied by ring opening and then recycclized of the intermediate gives the N-amino-2-quinolone compounds.

The structure of compounds (1, 5 and 9) was established on the bases of spectral data. Their IR spectra display absorption bands at (1645, 1665 and 1662 cm$^{-1}$) related to the (C=O) bond stretching, and (3270, 3272 and 3278 cm$^{-1}$) related to (N-H) bond stretching respectively.

The UV spectra showed absorption band at $\lambda_{\text{max}}$ (227-238 nm) due to the n $\rightarrow \pi^*$ transition.

Treatment of compounds (1, 5 and 9) with methyl acetoacetate in the presence of acid firstly afforded the hydrazide (as shown in eq. 2). These hydrazides were reacted with sodium acetate to give the carbanion which attacks the carbonyl carbon group of the pyridone ring with elimination of water molecule to give 3-acetyl-pyrazolo[1,5-a]-quinoline-2-one derivatives (2, 6 and 10) respectively.

The structure of the compounds (2, 6 and 10) was confirmed by means of IR, UV spectra in addition to the $^1$H-NMR spectrum for compound (2) as a sample for this series. The IR spectra show a (N-N) bond stretching at (1050, 1044 and 1049 cm$^{-1}$) respectively and there are two different bonds related to the two carbonyl compounds (1691, 1696 and 1701 cm$^{-1}$) for the acetyl carbonyl group respectively, and at (1670, 1685 and 1682 cm$^{-1}$) related to the lactam carbonyl group respectively. Other bands were illustrated in table (1).

The UV spectra of these compounds showed $\lambda_{\text{max}}$ bands at (245-255 nm) due to the n $\rightarrow \pi^*$ transitions.

The $^1$H-NMR spectrum of compound (2) shows the following peaks: 3.30 ppm (s, 3H, -CO-CH$_3$); 3.51 ppm (s, 3H, 5-CH$_3$) and 3.70 ppm (s, 3H, -OCH$_3$). The (NH) appears at 9.10
ppm. The peak at 6.51 ppm (s, 1H, 4-CH), and the three aromatic protons appears at a range (m, 7.10-7.65 ppm).

The reaction of N-amino-2-quinolones (1, 5 and 9) with ethyl acetimidate afforded the three derivatives of triazoloquinoline (3, 7 and 11), as in eq. (3).

![Chemical Structure]

The structure of the compounds (3, 7 and 11) was identified by using IR, UV spectra in addition to the ¹H-NMR spectrum for compound (7) as a sample for this series. The main bands in the IR spectra as in table (1) indicates the formation of (C=N) band due to appearance of bands at (1661, 1677, 1668 cm⁻¹) respectively, also indicate the disappearance of the carbonyl group absorption band. The UV spectra for these compounds showed λ_max at (247-256 nm) due to the n → π* transition.

The ¹H-NMR spectrum of compound (7) showed a multiplet peaks in a range (3.20-3.91 ppm) (9H) for the three methyl groups, 6.51 ppm (s, 1H, 4-CH) and 6.80 ppm (s, 1H, 8-CH), the peaks of the two aromatic protons appear in the range of (7.11-7.51 ppm).

Coumarin itself and its furo derivatives react with other amino derivatives like thiosemicarbazide through nucleophilic displacement to form triazoloquinoline-thione derivatives (4, 8 and 12) as in eq. (4).

![Chemical Structure]

The structure of the compounds (4, 8 and 12) were confirmed by using IR, UV spectra in addition to the ¹H-NMR spectrum for compound (12) as a sample for this series. The main absorption bands in the IR spectra as in table (1) indicate that the (C=N) band absorbed at (1636, 1616 and 1622 cm⁻¹) respectively, and showed a disappearance of the carbonyl group absorption band. Other absorption band at (1395, 1389 and 1388 cm⁻¹) related to (C=S) respectively. The (N-H) bond stretching appears at (3257, 3220 and 3205 cm⁻¹) respectively. Furthermore in the UV spectra of these compounds showed maximum absorption λ_max at (255-278 nm) this was attributed n → π* transition.

The ¹H-NMR spectrum of the compound (12) as a sample for this series shows three peaks of a nine protons of the three methyl groups at (3.31, 3.35 and 3.75 ppm); 6.50 ppm (s, 1H, 4-CH) and the two aromatic protons appears as a doublet at (7.22 and 7.61 ppm). The (NH) proton appears as singlet at 7.88 ppm.
### Table 1: The physical and spectral data of the prepared compounds.

<table>
<thead>
<tr>
<th>No.</th>
<th>m.p °C</th>
<th>UV (MeOH) λ\text{max} nm</th>
<th>IR (KBr) cm(^{-1})</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C=O</td>
</tr>
<tr>
<td>1</td>
<td>193-195</td>
<td>227</td>
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<tr>
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<td>12</td>
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</table>
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Scheme (1)

a = MeI
b = NH₂ - NH₂
c = Methyl acetoacetate
d = Ethyl acetimidate
e = Thiosemicarbazide
REFERENCES


