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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 ^{1}H-NMR.

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

تشييد بعض مركبات البايرازولو والترايازولو كوينولين الجديدة من مشتقات الكومارين

الملخص

استخدم الكومارين ومشتقاته من الفيوروكومارين مثل البسورالين والايزوبسورالين بصفة مواد اولية لتحضير بعض المركبات الحلقية غير المتجانسة.

فقد استخدمت المركبات (4-ميثل-7-ميثوكسي كومارين (II))، 6,4 – ثنائي مثيل بسورالين (III) و 9,8,4– ثلاثي مثيل ايزوبسورالين (IV) لتحضير المركبات (5,1 و9) من خلال تفاعلها مع الهيدرازين المائي في محيط قاعدي عبر التفاعل التعويضي النيكلوفيلي لتكوين مركبات N-امينو-2- كوينولون ومشتقاته من الفيوروكوينولون. عند تفاعل هذه المركبات (5,1 و9) مع اسيتواسيتات المثيل، اسيتوايميدات المثيل او الثايوسيميكاربازيد تتكون مركبات حلقية غير متجانسة مندمجة جديدة مثل البايرازولو- كوينولين

ومشتقاته من الفيوروكومينولين (6,2 و10)، ترايازولو-كومينولين ومشتقاته من الفيوروكومينولين (7,3 و11) او 4,2,1- ترايازولوكومينولين-2-ثايون ومشتقاته من الفيوروكومينولين (8,4 و12) على التوالي.

تم تشخيص المركبات المحضرة بالطرائق الفيزيائية والطيفية المتيسرة IR, UV وطيف الرنين النووي المغناطيسي.

الكلمات المفتاحية: مشتقات الكومارين، N-امينو-2- كومينولون، بايرازولوكومينولين و ترايازولو كومينولين.

INTRODUCTION

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

Coumarin and it is 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 (Katritizky *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.

spectrophotometer 2003. Ultraviolet (UV) spectra were preformed on Shimadzu UV-Visible spectrophotometer, UV-1650.^{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 firsr 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 stirrered for (4 hrs) at 130 ºC 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).

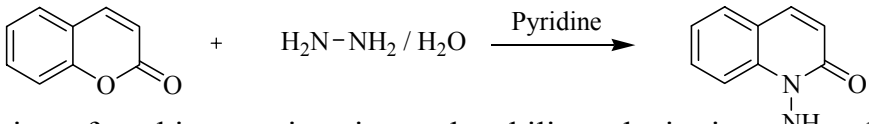
Ethyl acetimidate (1 mmole) [which prepared according to the published procedure (Vogel, 2007)] was added to a mixture of (30 ml) 10 % sodium carbonate solution and (30 ml) toluene to form two layers. The mixture was shaken then the organic layer was separated. To the organic layer N-amino-2-quinolone (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).

RESUITS AND DISCUSSION

The synthetic pathway leading to the title compounds is given in secheme (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 recyclized to form N-amino-2-quinolone derivatives as in (eq. 1) (Youssef *et al*., 2006).



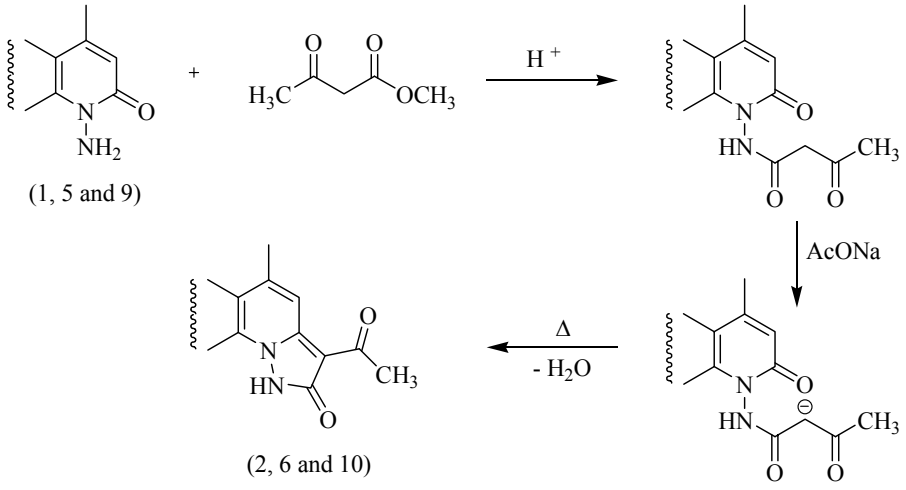
..... (eq. 1)

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 companied by ring opening and then recyclized 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 λ_{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.



(1, 5 and 9)

(2, 6 and 10)

..... (eq. 2)

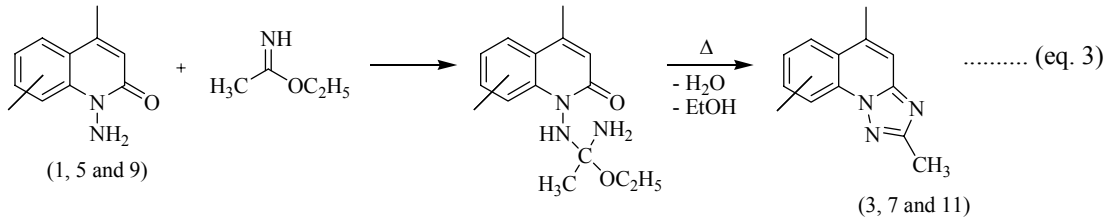
The structure of the compounds (2, 6 and 10) was confirmed by means of IR, UV spectra in addition to the ^{1}H-NMR spectrum for compound (2) as a sample for this series. The IR spectra show a (N-N) bond stretching at (1050, 1044 and 1049 cm^{-1}) respectively and there are two different bonds related 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 λ_{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).

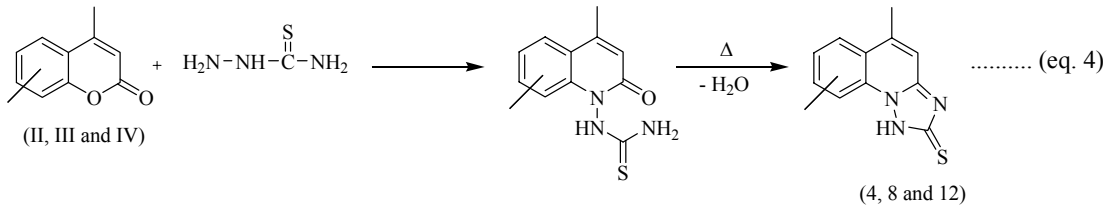
The reaction of N-amino-2-quinolones (1, 5 and 9) with ethyl acetimidate afforded the three derivatives of triazoloquinoline (3, 7 and 11), as in eq. (3).



..... (eq. 3)

The structure of the compounds (3, 7 and 11) was identified by using IR, UV spectra in addition to the ^{1}H-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 ^{1}H-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).



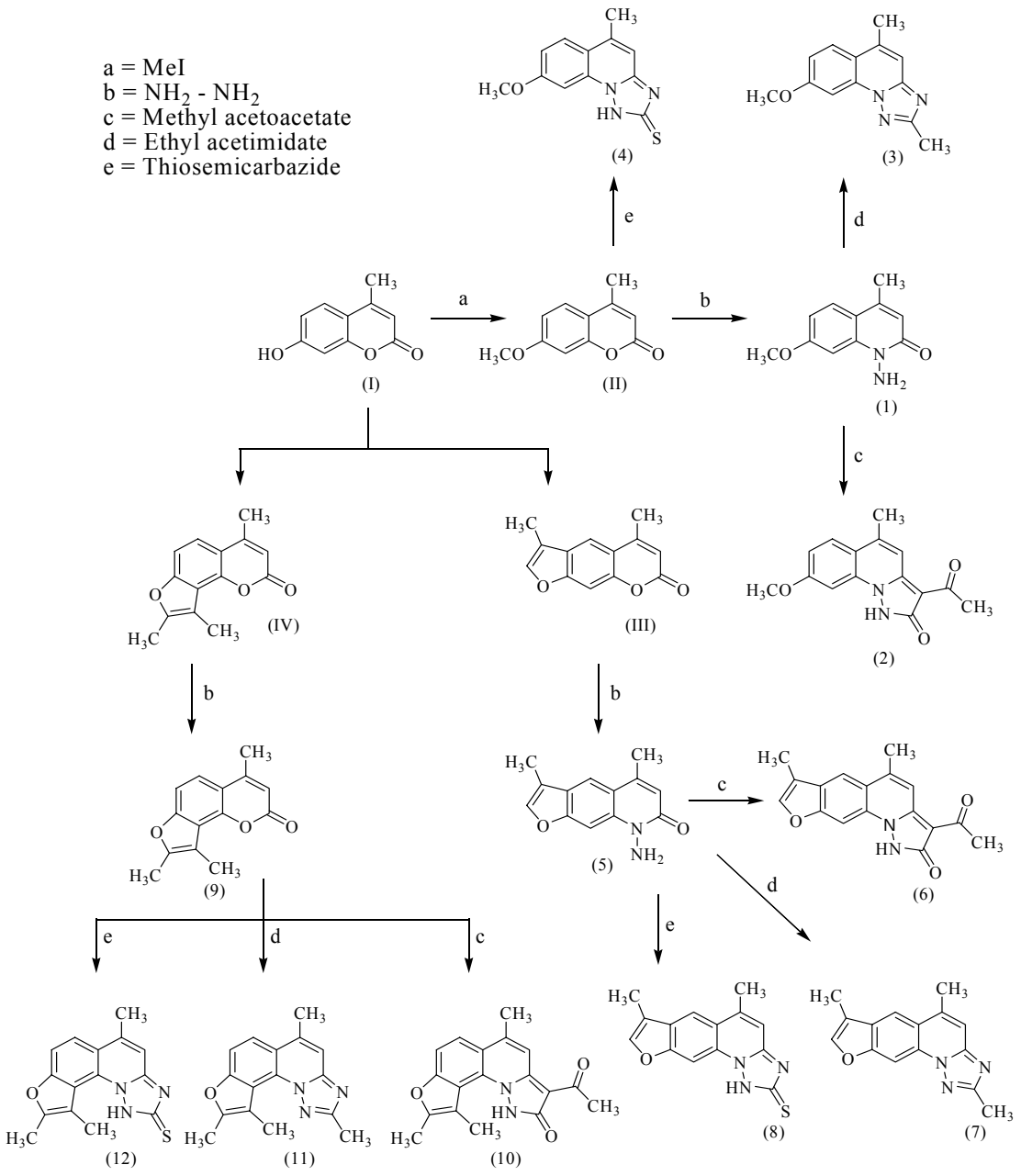
..... (eq. 4)

The structure of the compounds (4, 8 and 12) were confirmed by using IR, UV spectra in addition to the ^{1}H-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 ^{1}H-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.

No.	m.p °C	UV (MeOH) λmax nm	IR (KBr) cm^{-1}						
			C=O	C=C	C=N	C=S	N – N	N – H	C – O – C
1	193-195	227	1645	1595	….	….	1105	3270	1150
2	253-255	245	1670 1691	1562	….	….	1115	3217	1155
3	218-220	247	….	1601	1661	….	1126	3182	1156
4	117-119	255	….	1591	1636	1395	1141	3257	1178
5	240-242	236	1665	1688	….	….	1184	3272	1235
6	168-170	251	1685 1696	1610	….	….	1176	3210	1126
7	225-227	253	….	1570	1677	….	1132	3196	1180
8	222-224	270	….	1589	1616	1389	1184	3220	1210
9	167-169	238	1662	1602	….	….	1173	3278	1232
10	224-226	255	1682 1701	1618	….	….	1138	3222	1138
11	200-202	256	….	1582	1668	….	1125	3217	1185
12	153-155	278	….	1582	1622	1388	1112	3205	1177


a = MeI
b = NH2 - NH2
c = Methyl acetoacetate
d = Ethyl acetimidate
e = Thiosemicarbazide
(I)
(II)
(III)
(IV)
(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
(9)
(10)
(11)
(12)

Scheme (1)

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