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Heterocyclic Synthesis With Nitriles: Synthesis Of Some New Chromone and Flavone and Its Utilization For The Synthesis Of Potentially Antitumorigenic Polycyclic Chromones and Flavones

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HETEROCYCLIC SYNTHESIS WITH NITRILES: SYNTHESIS OF SOME NEW CHROMONE AND FLAVONE AND ITS UTILIZATION FOR THE SYNTHESIS OF POTENTIALLY ANTITUMORIGENIC POLYCYCLIC CHROMONES AND FLAVONES.

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A new synthesis of chromones and flavones based on the reaction of 2-hydroxy-1-acetonaphthone (1) with cinammonitriles (2 a-h) is described . Structures of the compounds are established by chemical and spectral data. This synthetic approach appears general in its applicability. It has been applied to the synthesis of a series of polycyclic chromone and flavone compounds containing the naphthalene and pyrene ring systems that hold promise as agents for the chemo preventation of cancer.

Flavones are known to play a vital role in plant life[1,2] . Many synthetic flavones are known to possess various physiological activities[3,4] . Some compounds of these classes, notably 5,6- and 7,8- benzoflavone and ellagic acid, have been shown to exhibit significant activity as inhibitors for tumor induction by carcinogenic polycyclic aromatic hydrocarbons (PAHs)[5] . In contrast to most other types of tumor- inhibitory compounds, many of which exhibit toxicity, mutagenicity, and other undesirable properties, the coumarin and chromone compounds tend to show minimal side effects[6]. It was, therefore, thought worthwhile to synthesize some new members of this series and test them for their biological activity.

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A majority of the naturally occurring flavones have mainly hydroxy and methoxy groups as substituents either in the benzenoid ring or at three position. For the past I have been exploring the synthetic potential, scope and limitation of activated nitriles in heterocyclic synthesis[7]. Several new approaches for the synthesis of five, six and their fused heterocyclic derivatives have been achieved during this work[8-13]. We now report extension of this novel synthetic approach to the preparation of chromones and flavones and utilization of the method to prepare a series of potentially antitumorigenic chromones and flavones. The synthetic route employed is based upon ready availability of cinnamonitriles (2 a-h) with 2-hydroxy-1-acetonaphthone (1). Reactions of this type have not been reported previously, but are found to give products in excellent yield under very mild conditions. Moreover, the resulting chromone and flavone derivatives have latent functional substituents which give potential for further chemical transformations and thus open up a new route for the preparation of substituted chromone and flavone derivatives with possible biological activity.

Thus, it has been found that compounds (2 a-h, X = COOEt) underwent reaction with 2-hydroxy-1-acetonaphthone (1) in boiling ethanol containing catalytic amounts of piperidine to give the benzoflavone derivatives (4 a-h). Structure (4) is suggested for the reaction product on the basis of both elemental and spectral analysis. The infrared spectrum of compound (4 a) showed absorption at 1660 cm^{-1} (CO), and the ^1H NMR spectrum revealed singlet at δ 2.43 ppm, assigned to methyl group, two doublet - doublet at δ 2.91 ppm and 3.20 ppm respectively assigned to the C_3 protons and doublet at δ 5.79 ppm for C_2 proton of the chromone and a multiplet at δ 7.14 -7.78 ppm assigned to the aromatic protons (cf. Table 2).

While the ^1H NMR spectra of (4 c) revealed mutually coupling resonance at δ 2.9 and 3.1 (dd, J = 2.6 Hz, 2H) and 5.6 (dd, J = 2.6 Hz, 1H), characteristic of a C_3- H and C_2-H protons respectively . Additionally, the ^{13}C NMR spectrum exhibited fifteen resonances in the aromatic region (δ 112.60-163.19 ppm) and three at 76, 45, 192 ppm, characteristic of the C_2, C_3 and C_4 carbon atoms

Table 1 Characterization Data of The Newly Prepared Compounds

Cpd No.	Aryl (**2**)	Lett. Desi	m.p. °C	Yld %	Anal. Calcd. (found)
4	C_6H_4 -CH_3 - o	a	178	88	C, 83.31(83.29); H, 5.55(5.54)
4	C_6H_2 - OCH_3 - o,m,p	b	130	85	C, 72.51 (72.50); H, 5.49 (5.48)
4	Pyridyl- m	c	120	84	C, 78.54 (78.49); H, 4.72 (4.71); N, 5.09 (5.08)
4	C_6H_3- OCH_3- o,m	d	116	86	C, 75.44 (75.41); H, 5.38 (5.36)
4	C_6H_3- OCH_3- o,Br-m	e	146	89	C, 62.67 (62.64); H, 3.91 (3.89)
4	C_6H_4- F- m	f	112	92	C, 78.08 (78.02); H, 4.45 (4.41)
4	Pyrolyl-o, N- CH_3	g	152	90	C, 77.97 (77.95); H, 5.41 (5.40); N,5.05 (5.00)
4	Thionylyl-o	h	138	94	C, 72.85 (72.82); H, 4.28 (4.26)
5	C_6H_4- CH_3- o	a	220	60	C, 83.91 (83.89); H, 4.89 (4.88)
5	C_6H_2- OCH_3- o,m, p	b	285	63	C, 72.92 (72.90); H, 4.97 (4.94)
5	Pyridyl- m	c	192	66	C,79.12 (79.11); H, 4.02 (4.00); N, 5.12 (5.11)
5	C_6H_3- OCH_3- o,m	d	310	65	C, 75.90 (75.89); H, 4.81 (4.80)
5	C_6H_3- OCH_3- o,Br-m	e	210	68	C, 63.00 (62.98); H, 3.41 (3.40)
5	C_6H_4- F- m	f	302	66	C, 78.62 (78.60); H, 3.79 (3.76)
5	Pyrolyl-o, N- CH_3	g	205	67	C, 78.54 (78.53); H, 4.72 (4.70); N, 5.09 (5.05)
5	Thionylyl-o	h	250	65	C, 73.38 (73.35); H, 3.59 (3.53)
7	C_6H_4 -CH_3 - o	a	268	68	C, 82.14 (82.11); H, 4.76 (4.74)
7	C_6H_2 - OCH_3 - o,m, p	b	310	65	C, 72.81 (72.80); H, 4.85 (4.84); N, 6.79 (6.75)
7	Pyridyl- m	c	226	60	C, 78.01 (77.99); H, 4.02 (4.00); N, 13.00 (12.89)
7	C_6H_3- OCH_3- o,m	d	276	62	C, 75.39 (75.36); H, 4.31 (4.30); N,7.32 (7.31)
7	C_6H_3- OCH_3- o,Br-m	e	300	60	C, 64.05 (64.03); H, 3.49 (3.48); N, 6.49 (6.41)
7	C_6H_4- F- m	f	330	61	C, 77.64 (77.63); H, 3.82 (3.79); N,8.23 (8.21)

Table 2 Spectral Data of The Newly Prepared Compounds

Cpd No.	IR (ν Cm^{-1})	NMR (δ ppm)
4a	1657, 1604, 1570, 1512	2.4(s,3H,CH_3),2.91(dd,J=2.6Hz,1H,C_3-C_2), 3.20(dd,J=2.6Hz,1H,C_3-C_2), 5.79(dd,J=2.6Hz,1H,C_2-C_3),7.14-7.78(m,8H,Ar-H),9.51(d,2H,C_9 andC_{10})
4b	1670,1597, 1570, 1512	3.93 (s,3H,OCH_3), 3.88 (s,3H,OCH_3), 3.87 (s,3H,OCH_3), 2.91(dd, J=2.6 Hz,1H,C_3-C_2), 3.20 (dd, J=2.6 Hz, 1H,C_3-C_2),5.79(dd, J=2.6Hz,1H,C_2-C_3),7.13-7.73(m,6H, Ar-H), 9.50(d,2H,C_9 and C_{10})
4c	1656,1604, 1570, 1512	2.94(dd,J=2.6Hz,1H,C_3-C_2),3.15(dd, J=2.6 Hz,1H,C_3-C_2),5.60(dd, J= 2. 6 Hz,1H,C_2-C_3),7.12-7.91(m,8H,Ar-H),8.75 (s,1H,Py-H), 9.43(d,2H,$C_9$and C_{10})
4d	1657,1604, 1570, 1512	3.79 (s,3H,OCH_3), 3.81 (s,3H,OCH_3), 2.91(dd, J=2.6 Hz, 1H, C_3-C_2), 3.03 (dd, J=2.6 Hz, 1H,C_3-C_2),5.92(dd, J=2.6Hz, 1H, C_2-C_3),6.84-7.74(m,7H, Ar-H), 9.50(d,2H,C_9 and C_{10})
4e	1657,1604, 1570, 1512	3.83(s,3H,OCH_3),2.83(dd,J=2.6Hz,1H,C_3-C_2),3.29(dd,J=2.6 Hz,1H,C_3- C_2) 5.91(dd, J=2.6Hz,1H,C_2-C_3),7.07-7.92(m,7H,Ar-H),9.36(d,2H,$C_9$and C_{10})
4f	1657,1604, 1570, 1512	2.94(dd, J=2.6 Hz, 1H, C_3-C_2), 3.35 (dd, J=2.6 Hz, 1H,C_3-C_2),5.82(dd, J=2.6Hz, 1H, C_2-C_3),7.23-7.92(m,8H, Ar-H), 9.37(d,2H,C_9 and C_{10})
4g	1657,1604, 1570, 1512	3.11(dd,J=2.6 Hz,1H,C_3-C_2),3.40(dd,J=2.6 Hz,1H,C_3-C_2),3.75 (s,3H,CH_3), 5.64(dd,J=2.6Hz,1H,C_2-C_3), 6.17-7.75 (m,7H,Ar-H), 9.48(d,2H,$C_9$and C_{10})
4h	1657,1604, 1570, 1512	3.09(dd, J=2.6 Hz, 1H, C_3-C_2), 3.29 (dd, J=2.6 Hz, 1H,C_3-C_2),5.77(dd, J=2.6Hz, 1H, C_2-C_3),7.01-7.75(m,7H, Ar-H), 9.48(d,2H,C_9 and C_{10})
5a	1650,1640, 1618, 1585	2.43(s,3H,CH_3),6.85(s,1H,C_3),7.34-8.16(m,8H,Ar-H),8.85(d,2H,C_9andC_{10})
5b	1658,1635, 1584	3.93 (s,3H,OCH_3), 3.88 (s,3H,OCH_3), 3.87 (s,3H,OCH_3), 6.86(s,1H,C_3), 7.24-7.89(m,6H, Ar-H), 8.65(d,2H,C_9 and C_{10})
5c	1656,1640, 1616, 1585	6.84(s,1H,C_3), 7.42-7.93(m,7H, Ar-H), 8.65(d,2H,C_9 and C_{10}), 8.75 (s, 1H,Py-H)
5d	1656,1640, 1585	3.79 (s,3H,OCH_3), 3.81 (s,3H,OCH_3), 6.85(s,1H,C_3), 7.23-7.84(m,7H, Ar-H), 8.34(d,2H,C_9 and C_{10})
5e	1655,1643, 1588	3.83 (s,3H,OCH_3), 6.84(s,1H,C_3), 7.15-7.77(m,7H, Ar-H), 8.45(d,2H,C_9 and C_{10})
5f	1656,1636, 1618	6.85(s,1H,C_3), 7.32-7.93(m,8H, Ar-H), 8.42(d,2H,C_9 and C_{10})
5g	1659,1638, 1616, 1581	3.75(s,3H,CH_3), 6.33-7.82(m,7H, Ar-H), 6.86(s,1H,C_3), 8.32(d,2H,C_9 and C_{10})
5h	1658,1636, 1616, 1585	6.85(s,1H,C_3), 7.21-7.80(m,7H, Ar-H), 8.54(d,2H,C_9 and C_{10})
7a	3450,2220, 1618, 1574	2.44 (s,3H,CH_3), 7.16-7.54(m,8H, Ar-Hand OH),7.74 (s, 1H,C_3), 8.52(s,1H,C_6), 8.85(d,2H,C_9 and C_{10})
7b	3450,2220, 1618, 1574	3.91 (s,3H,OCH_3), 3.87 (s,3H,OCH_3), 3.84 (s,3H,OCH_3), 7.44(s,1H,C_3), 7.53-8.24(m,6H,Ar-H and OH),8.52(s,1H,C_6), 8.86 (d, 2H ,C_9 and C_{10})
7c	3450,2220, 1618, 1575	7.07-7.85(m,8H, Ar-H and OH), 8.15(s,1H,C_3), 8.54(s,1H,C_6), 8.86 (d, 2H ,C_9 and C_{10})
7d	3450,2220, 1618,1575	3.78 (s,3H,OCH_3), 3.90 (s,3H,OCH_3), 7.42-7.94 (m,7H,Ar-H and OH), 8.14 (s,1H,C_3),8.52(s,1H,C_6), 8.75 (d, 2H ,C_9 and C_{10})
7e	3450, 2220, 1618, 1575	3.90 (s,3H,OCH_3),7.12(s,1H,C_3), 7.43-8.21(m,7H, Ar-H and OH), 8.52(s,1H,C_6), 8.81 (d, 2H ,C_9 and C_{10})
7f	3450,2220, 1618, 1575	7.29-8.09 (m,8H,Ar-H and OH), 8.19 (s,1H,C_3),8.48(s,1H,C_6), 9.00 (d, 2H ,C_9 and C_{10})

respectively in the pyrone ring, and the IR spectrum showed an carbonyl absorption band at 1656 cm^{-1} .The structure of (4 c) was also confirmed by X- ray diffractometry. The identification and location of the atoms in (4 c) are shown in the ORTEP[14] drawing (see FIG 1).

The formation of compound (4) is assumed to proceed via the Michael addition of the hydroxyl group of (1) to the cinnamonitrile (2) to yield the intermediate (3) which readily undergoes cyclization to give the flavone derivative (4).

Attempted dehydrogenation of (4) with various reagents commonly employed for this purpose such as DDQ and SeO_2 gave the chromone (5) in good yield . Structure (5) is supported by the infrared spectrum which revealed CO absorption at 1658 cm^{-1} and the ^1H NMR spectrum showed singlet C_3-H proton at δ 6.85 ppm. In addition to that, it was found that, compound (1) reacted with (2 a-h, X= CN) in ethanolic piperidine to afford a mixture of 7,8-benzoflavone (4 a-f) and a polysubstituted pyridine (7 a-f) in a different ratio depending on the nature of the cinnamonitrile reagent . The structure of (7 a-f) was established on the basis of IR and ^1H NMR spectra . Its ^1H NMR spectrum showed a signal at δ 8.5 ppm for pyridine H-2 . Absence of a signal for methyl protons provided an evidence for the involvement of the acetyl group in the reaction.

The formation of (7) is assumed to proceed via the intermediate (6) . The methods outlined in Schemes 1 and 2 provides convenient synthetic access to chromone and flavone derivatives from readily available cinnamonitrile and 2-hydroxy-1-acetonaphthone under mild conditions. Studies of the anticarcino geniproperties of these compounds will be under taken followingcompletion of studies of the analogous polycyclic coumarins that are currently in progress.

Experimental

All m.ps uncorrected. FTIR spectra ($CHCl_3$) were record on Nicolet Magna-IR model 550 spectrophotometer, the NMR spectra on Brucker Wpsy-200MHz spectrometer using TMS as internal standard chemical shifts in δ, ppm) .

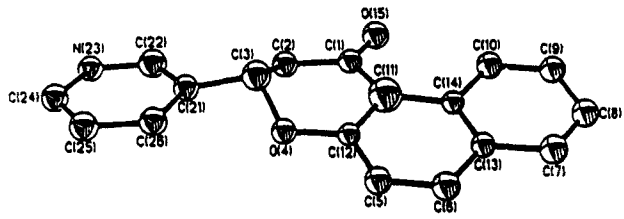
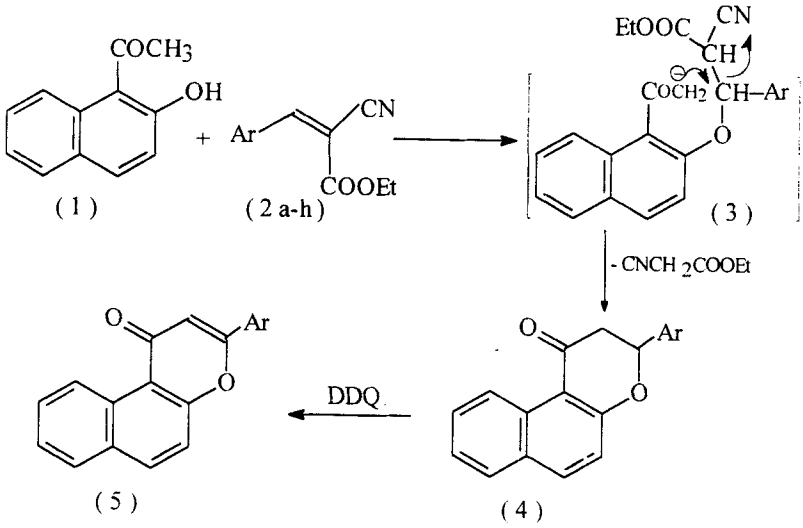


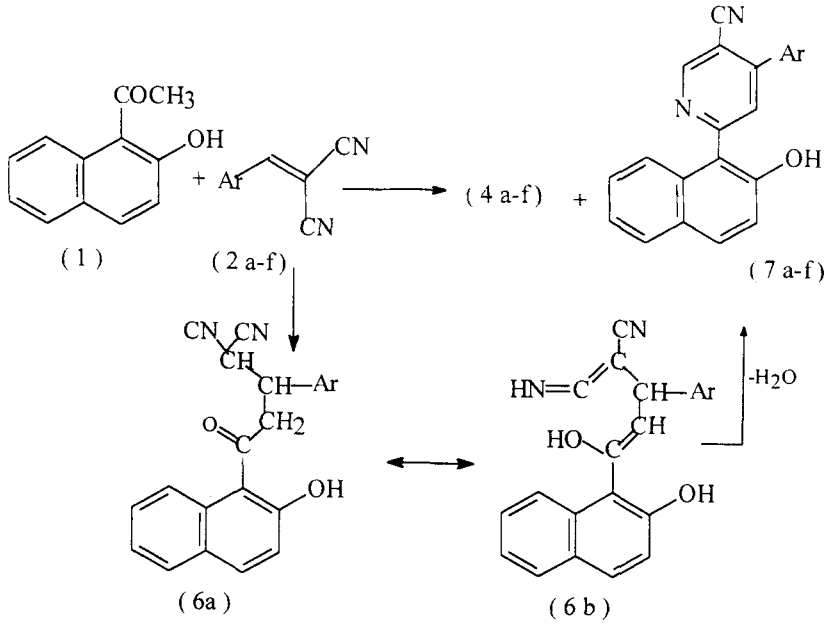
FIG 1



Scheme 1

Reaction of 2- hydroxy-1- acetonaphthone (1) with cinnamonitrile (2 a-h, X= COOEt) . A preparation of 7,8-benzoflavone (4 a-h).

A mixture of 2- hydroxy-1- acetonaphthone (1) (0.01 mol). 2 a-h (X=$COOC_2H_5$, 0.01 mol) and catalytic amount of piperidine (0.1 mL) in ethanol (15 mL) was refluxed for 6 hr. The solid product obtained after cooling was filtered and crystallized from a suitable solvent to give (4 a-h) .



Scheme 2

General procedure for the preparation of flavones (5 a-h) .

To a stirred solution of (4 a-h, 0.01 mol) in benzene (10 mL) was added DDQ (0.01 mol) in benzene (10 mL). The reaction mixture was refluxed with stirring for 6 hr. the solid obtained was filtered while hot and recrystallized from a suitable solvent to give (5 a-h) .

Reaction of 2- hydroxy-1- acetonaphthone (1) with cinnamonitrile (2 a-h, X= CN). A preparation of 7,8-benzoflavone (4 a-h) and 5-cyano-1-(2-hydroxy naphthyl)-4-aryl pyridine (7 a-f) .

A mixture of 2- hydroxy-1- acetonaphthone (1) (0.01 mol), 2 a-h (X = CN, 0.01 mol) and catalytic amount of piperidine (0.1 mL) in ethanol (15 mL) was refluxed for 6 hr. the solid obtained was filtered while hot and recrystallized from a

suitable solvent to give (7 a-f) , the filtrate was cooled and recrystallized from a suitable solvent to give (4 a-f) .

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