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Synthesis and characterization of some novel coumarin based various 2-aryl-pyrido [3,2-*c*] coumarins

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ABSTRACT

A survey of the literature reveals that the number of coumarin derivatives having heterocyclic moieties either as substituent groups or fused with parent coumarin nucleus possesses a variety of functions and are widely used in drugs and dyes. Because of this wide utility, the synthesis of coumarin has remained a subject of active interest. Looking at the importance of these heterocoumarins and with a view to exploring new methods of their synthesis, the present work was undertaken and this synthesis deals with various 2-aryl-pyrido [3,2-*c*] coumarins. The compounds have been synthesized by reacting Mannich bases of various 4-hydroxy coumarins with pyridinium salts of various aroyl methyl bromides in the presence of ammonium acetate and acetic acid. All the compounds synthesized have been characterized by analytical and spectral data.

Keywords: Pyrido, Coumarins, Krohanke's reaction.

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INTRODUCTION:

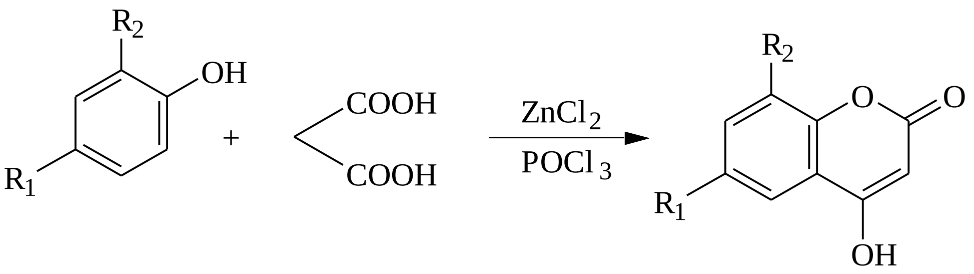
The work incorporated in this series of synthesis of various 2-aryl-pyrido [3,2-*c*] coumarins. The compounds have been synthesized by reacting appropriate Mannich bases of 4-hydroxy coumarins with various aroyl methyl pyridinium bromide salts in the presence of ammonium acetate and acetic acid utilizing Krohnke's mechanism. The structures of all the 2-aryl-pyrido [3, 2-*c*] coumarins synthesized have been supported by analytical and spectral data.

A literature survey reveals that a very large number of coumarin derivatives containing heterocyclic moieties are used in drugs and dyes. The varied biological activities of the coumarins fused with other heterocycles have encouraged researchers with regard to the procedures and substrates, improving the feasibility of broad families of these compounds. Several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to a pyridine ring. For instance, the coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors [1] such as topoisomerase II [2] and tyrosine kinase [3] inhibitors. Coumarins joined to pyridines have been reported to possess antiallergic [4], anticoagulant [5], antidiabetic [6] activities, and even analgesic [7] properties, being characterized by phenanthrene like structure as found in tetrahydrocannabinol. The pyrido [2,3-*c*]coumarin skeleton constitutes the backbone of Santiagonamine [8]. This alkaloid has been isolated from Berberis Darvinii (Berberidaceae) and has shown interesting wound healing properties [9-15].

Thus pyrido fused coumarins become an important class of heterocyclic fused coumarin derivatives and therefore brief literature account on various synthetic methods available for pyrido fused coumarins are presented in research work

Experimental

2.1 Preparation of 4-hydroxy coumarin, 6-methyl-4-hydroxy coumarin and 8-methyl-4-hydroxy coumarin (1a-c).



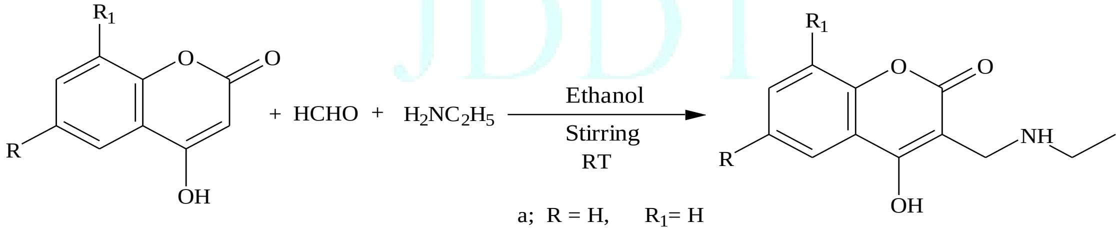
In a 500 ml round bottom flask attached with a reflux condenser and gas absorption trap, a mixture of appropriate phenol (0.2 mole), malonic acid (22g, 0.2 mole), anhydrous zinc chloride (80g, 0.6 mole) and phosphorous oxychloride (60 ml, 0.4 mole) was heated with stirring at 60-65 ^{o}C for 35 hours. The yellow coloured mixture was cooled and decomposed with water and left overnight. The resulting crude 4-hydroxy coumarin was filtered out, washed with water and dried. This crude product was purified by dissolving it in 10% sodium bicarbonate solution, filtering and reprecipitating by adding dilute HCl solution. The 4-hydroxy coumarin was separated out as a yellowish-white solid. This was filtered out, washed with water, dried and recrystallized from ethanol-water.

2.2 Preparation of 6-chloro-4-hydroxy coumarin (1d).

In a 250 ml round bottom flask fitted with reflux condenser, a mixture of p-chloro phenol (25.6g, 0.2 mole), malonic acid(10.4g, 0.1mole) and phosphorous oxychloride $POCl_3$ (30.4 ml) was placed. The reaction mixture was heated for 30 minutes on boiling water bath. It was cooled and poured into ice cold water. The white solid obtained was filtered and washed with cold water. It was then washed with saturated sodium bicarbonate solution to remove unreacted malonic acid. Finally it was washed with water and dried. Thus diester $[CH_2(CO_2Ph\text{-}pCl)_2]$ obtained was recrystallized from ether-hexane. Yield 22g, 68%, m.p. 115^{0}C.

The above diester (20g) and anhydrous aluminum chloride (20.6g) were taken in a round bottom flask. The flask was stoppered and shaken vigorously for 2-3 minutes. A reflux condenser provided with gas absorption tube was attached and the flask was heated in an oil bath at 180-185°C for 30 minutes. The reaction mixture was allowed to cool to room temperature and then flask was immersed in an ice bath. The reaction mixture was decomposed by dilute HCl (1:7) over a period of about 2 hours. The content was then heated on steam bath for 30 minutes with vigorous stirring in order to effect the complete decomposition. The solid product obtained was filtered out and washed with water and dried. The product was then dissolved in 5% aqueous sodium hydroxide solution and the solution was filtered. The product was then reprecipitated by adding dilute HCl, until solution was acidic. The precipitates were filtered out, washed with water and dried. It was recrystallized from ethyl acetate-hexane.

2.3 Preparation of Mannich bases of 4-hydroxy coumarins(1a-d).



a; R = H, R_1= H
b; R = CH_3, R_1= H
c; R = H, R_1= CH_3
d; R = Cl, R_1= H

1(a-d)

In a 100 ml round bottom flask equipped with magnetic stirrer, formaldehyde (37% formalin solution) (0.025mole) and ethyl amine (0.03mole) were taken with ethanol (25ml) and stirred for 30 minutes. Thenafter an appropriate 4-hydroxy coumarin (0.025mole) dissolved in ethanol (15ml) was added dropwise to above well stirred solution during 30 minutes at room temperature. The reaction mixture was further stirred at room temperature for overnight. The solid obtained was filtered out and washed with ether and dried. The products were enough pure and were directly used for further reaction.

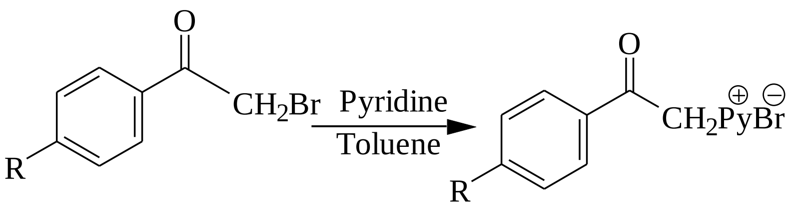
2.4 (i) Preparation of phenacyl bromide.

A solution of acetophenone (40g, 0.33 mole) in anhydrous ether (60 ml) was placed in a three necked flask equipped with a dropping funnel and a gas absorption tube. The flask was placed in an ice bath and was allowed to cool to 0-5^{0}C. A trace amount of anhydrous $AlCl_3$ (0.1g) was introduced and bromine (52.8g, 0.33 mole) was added drop wise with stirring during 30 minutes. The reaction mixture was allowed to come to room temperature and was stirred further for 1 hour. Then pet.ether (40-60^{0}C) (100 ml) was added. The phenacyl bromide was separated out as white solid. It was filtered out and was washed with a mixture of pet. ether (40-60 ^{0}C) and water (100 ml, 1:1). It was dried and recrystallized from rectified spirit.

2.4 (ii) Preparation of substituted phenacyl bromides.

An appropriate acetophenone (0.5 mole) in acetic acid (100 ml) was taken in a three necked flask equipped with a dropping funnel and a condensor with gas absorption tube. Bromine (0.5 mole) was added gradually from dropping funnel with stirring at room temperature during 30 minutes. The reaction mixture was stirred for 2 hours at room temperature. It was then poured into ice cold water (500 ml). The substituted phenacyl bromide was separated out as white solid. It was filtered out and washed with water and dried. It was recrystallized from rectified spirit. The following phenacyl bromides were prepared.

2.5 Preparation of aroyl methyl pyridium salts (2a-d).

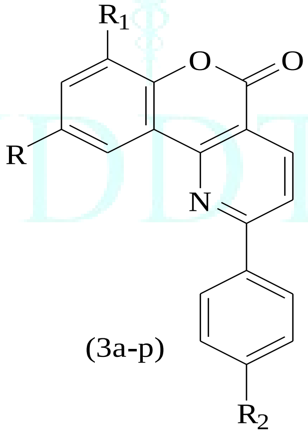


(2a-d)

An appropriate phenacyl bromide (0.25 mole) was dissolved in dry toluene (100 ml) at room temperature. Dry pyridine (0.25 mole) was added slowly to the above solution. The reaction mixture was then heated at 100 ^{0}C for 30 minutes. It was then allowed to come to room temperature. Phenacyl bromide pyridinium salt was separated out as a white solid. It was filtered out and washed with dry toluene. It was dried at 60-70 ^{0}C for 4-5 hours.

2.6 Synthesis of 2-aryl-pyrido [3, 2-*c*]coumarins (3a-p).

In a 100 ml round bottom flask equipped with a magnetic stirrer, aroyl methyl bromide pyridinium salt (2) (0.006mole) in glacial acetic acid (20ml) was taken. To this ammonium acetate (0.06mole) was added with stirring at room temperature. Then a solution of appropriate Mannich base of 4-hydroxy coumarin (1) (0.006mole) in glacial acetic acid (20ml) was added with stirring at room temperature for 15 minutes and the reaction mixture was further stirred for 1 hour at room temperature. Then after the reaction mixture was refluxed for 8 hours at 140 ^{o}C. It was then allowed to come to room temperature and was poured into ice-cold water. A sticky mass was separated out which was then extracted with chloroform (3x30ml). The chloroform layer was then washed with 5% $NaHCO_3$ and then with water. It was then dried over anhydrous sodium sulphate. The chloroform was removed under reduced pressure. The gummy residue obtained was subjected to column chromatography using silica gel and ethyl acetate-compounds thus obtained were recrystallized from chloroform-hexane.

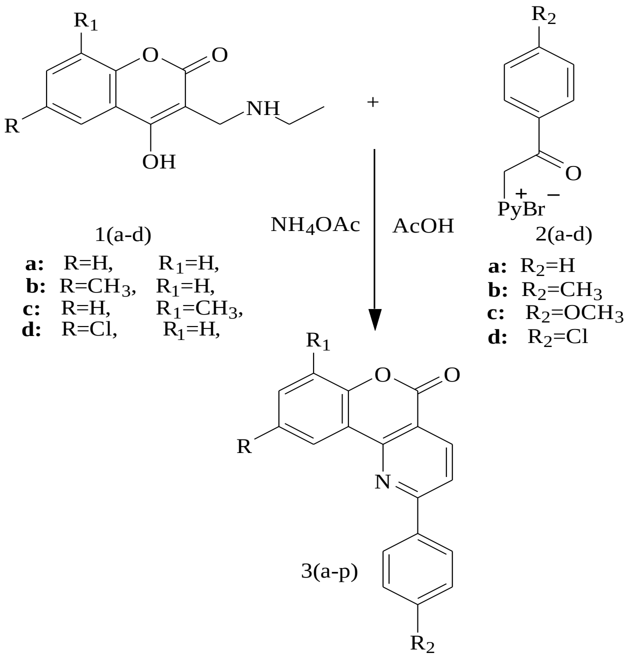


(3a-p)

RESULT AND DISCUSION

The new method developed in our laboratory for the synthesis of 2-aryl-pyrido [3, 2-*c*]coumarins, 4-hydroxy coumarin were reacted with the Mannich base of acetophenone under Krohnke's reaction condition. The tautomeric form of 4-hydroxy coumarin undergoes Michael addition with vinyl aroyl ketone, generated insitu from the Mannich base and gives the 1,5-dione intermediate which gets converted into the product in the presence of the $NH_4OAc/AcOH$ under Krohnke's reaction condition. Now it is interesting that the compound can also be synthesized by interchanging the functionality of the reacting components. i.e if a Mannich base of the 4-hydroxy coumarin is reacted with the aroyl methyl pyridinium salt under Krohnke's reaction condition, the product obtained will be the same. The Mannich base of the 4-hydroxy coumarin generates the intermediate, coumarin quinone methide which provides the α, β-unsaturated carbonyl system and Michael addition of aroyl methyl pyridinium salt converts it into a 1,5-dione intermediate which finally gives the product. The research work of is utilized and various 2-aryl-pyrido [3,2-c] coumarine has been synthesized.

The condensation of various Mannich bases (1a-d) with appropriate aroyl methyl pyridinium salts (2a-d), in the presence of ammonium acetate and acetic acid under Krohanke's reaction condition, gave the 2-aryl-pyrido[3,2-*c*]coumarins (3a-p).



a: R = H,	R_1 = H,	R_2 = H
b: R = H,	R_1= H,	R_2 = CH_3
c: R = H,	R_1= H,	R_2 = OCH_3
d: R = H,	R_1= H,	R_2 = Cl
e: R = CH_3,	R_1= H,	R_2 = H
f: R = CH_3,	R_1= H,	R_2 = CH_3
g: R = CH_3,	R_1= H,	R_2 = OCH_3
h: R = CH_3,	R_1= H,	R_2 = Cl
i: R = H,	R_1= CH_3,	R_2 = H
j: R = H,	R_1= CH_3,	R_2 = CH_3
k: R = H,	R_1= CH_3,	R_2 = OCH_3
l: R = H,	R_1= CH_3,	R_2 = Cl
m: R = Cl,	R_1= H,	R_2 = H
n: R = Cl,	R_1= H,	R_2 = CH_3
o: R = Cl,	R_1= H,	R_2 = OCH_3
p: R = Cl,	R_1= H,	R_2 = Cl

Among the Mannich bases of 4-hydroxy coumarins 1(a-d) used, 1a was known and hence its formation was confirmed by comparison of its melting point with the literature melting point. The (1b, 1c, 1d), were new and their structures were supported by analytical and spectral data.

Compound 1b

IR: ν_{max} 1720 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1605cm^{-1} (aromatic C=C stretching), 3365cm^{-1}(O-H stretching), 3325cm^{-1}(N-H stretching), 2960cm^{-1} (aliphatic C-H stretching), 3045cm^{-1} (aromatic C-H stretching).

NMR: 0.9-1.5δ (3*H*, triplet,-CH_2-CH_3), 2.3δ (3H, singlet, Ar-CH_3), 2.6-3.6δ (2*H* quartet, -CH_2-CH_3), 4.0δ (2*H*, singlet,-CH_2-NH), 6.8-8.1δ (5*H*, multiplet,three aromatic protons +, -NH and –OH protons merged).

Compound 1c

IR: ν_{max} 1710 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1600cm^{-1}(aromatic C=C stretching), 3360cm^{-1}(O-H stretching), 3340cm^{-1}(N-H stretching), 2935cm^{-1} (aliphatic C-H stretching), 3055cm^{-1}(aromatic C-H stretching).

NMR: 0.9-1.6δ (3*H*, triplet, CH_2-CH_3), 2.4δ (3*H*, singlet, Ar-CH_3), 2.7-3.4δ (2*H*, quartet, -CH_2-CH_3), 4.0δ (2*H*, singlet,-CH_2-NH), 6.8-8.0δ (5*H*, multiplet, three aromatic protons + -NH and –OH protons merged).

Compound 1d

IR: ν_{max} 1715 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1}(aromatic C=C stretching), 3370cm^{-1}(O-H stretching), 3315cm^{-1}(N-H stretching), 2950cm^{-1}(aliphatic C-H stretching), 3040cm^{-1} (aromatic C-H stretching).

NMR: 0.8-1.6δ (3*H*, triplet, $-CH_2-CH_3$), 2.5-3.7δ (2*H*, qurtet, $-CH_2-CH_3$), 4.0δ (2*H*, singlet, $-CH_2-NH$), 6.8-8.4δ (5*H*, multiplet, three aromatic protons + -NH and –OH protons merged).

All aroyl methyl pyridinium bromide salts (2a-d) were prepared by using literature method.

The condensation of Mannich bases of 4-hydroxy coumarins (1a-d) with aroyl methyl pyridinium bromide salts (2a-d) under Krohnke's reaction condition proceeded smoothly and gave the expected 2-aryl-pyrido[3,2,-*c*]coumarin (3a-p) in 55-61 % yield. The structures of all compounds (3a-p) were confirmed by analytical and spectral data.

Thus the reaction of Mannich base of 4-hydroxy coumarin (1b) with aroyl methyl pyridinium bromide salt (2c) gave the expected 2-aryl-pyrido [3,2,-*c*]coumarin (3g) as yellow solid product.

The IR spectrum of compound (3g) showed a strong band at 1715 cm^{-1} which is due to carbonyl stretching of lactone ring present in coumarin nucleus. The bands observed at 1610 cm^{-1} and 1430cm^{-1} can be assigned to aromatic C=C and C=N stretching vibrations respectively. Compound showed bands at 1235cm^{-1} and 1040cm^{-1} which can be attributed to asymmetric and symmetric C-O-C stretching due to the methoxyl group present in the phenyl ring. Compound showed a medium band at 835cm^{-1} which can be assigned to C-H banding vibration for p-disubstituted phenyl ring present at C_2. The compound showed bands at 2930cm^{-1} and 3030cm^{-1} which can be assigned to aliphatic C-H stretching of methyl group attached at C_9 and aromatic C-H stretching respectively.

The PMR spectrum (60MHz) of compound (3g) showed a singlet 2.5δ is due to three protons of methyl group present at C_9. A methoxyl signal appeared as a singlet at 3.9δ. A multiplet observed between 7.0-9.2δ (9H) is due to nine aromatic protons.

The structure of (3g) was further supported by high resolution PMR (300MHz) and ^{13}C spectral data. The PMR (300MHz) spectrum of compound (3g) showed a singlet at 2.49δ (3H). This is due to methyl protons attached at C_9. A methoxyl signal appeared at 3.90δ (3H) as a singlet. A multiplet observed between 7.04-8.54δ (9H) is due to nine aromatic protons.

A signal appeared at 21.12δ is due to methyl carbon attached at C_9. A signal appeared at 56.61δ is for carbon of $-OCH_3$ present in the compound. The signals appeared at 114.62, 117.13, 118.43, 119.48, 124.80, 126.23, 129.95, 130.63, 133.23, 134.66, 136.83, 138.02, 138.98, 151.29, and 151.95δ, corresponding to fifteen carbons is due to aromatic carbons. The most down field signal appeared at 162.34δ can be assigned to the carbonyl carbon of the δ-lactone ring of coumarin. In the absence of ^{13}C DEPT spectra the assignment of primary, secondary and tertiary carbons was not possible.

The IR and PMR (60MHz) spectral data for the other compounds (3a-p) are given below.

Compound 3a

IR: ν_{max} 1725 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1} and 1440cm^{-1} (C=C and C=N stretching), 3035cm^{-1}(aromatic C-H stretching).

NMR: 7.2-9.0δ (11*H*, multiplet, aromatic protons).

Compound 3b

IR: ν_{max} 1720 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1600cm^{-1} and 1435cm^{-1} (C=C and C=N stretching), 2950cm^{-1} (aliphatic stretching of methyl group), 3045cm^{-1} (aromatic C-H stretching).

NMR: 2.4δ (3*H*, singlet, $-CH_3$), 7.1 -9.0δ (10*H*, multiplet, aromatic protons).

Compound 3c

IR: ν_{max} 1725 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1} and 1440cm^{-1}(C=C and C=N stretching), 1245cm^{-1} (C-O-C stretching), 3035cm^{-1}(aromatic C-H stretching).

NMR: 3.8δ(3*H*, singlet,$-OCH_3$),7.0-8.8δ(10*H*,multiplet,aromatic protons).

Compound 3d

IR: ν_{max} 1710 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1615cm^{-1} and 1445cm^{-1}(C=C and C=N stretching), 3045cm^{-1}(aromatic C-H stretching).

NMR: 7.1-9.0δ (10*H*, multiplet, aromatic protons).

Compound 3e

IR: ν_{max} 1700 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1605cm^{-1} and 1430cm^{-1}(C=C and C=N stretching), 2945cm^{-1}(aliphatic C-H stretching of methyl group), 3040cm^{-1}(aromatic C-H stretching).

NMR: 2.4δ(3*H*,singlet,$-CH_3$),7.1-9.0δ (10*H*, multiplet, aromatic protons).

Compound 3f

IR: ν_{max}1710cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1605cm^{-1} and 1435cm^{-1}(C=C and C=N stretching), 2935cm^{-1}(aliphatic C-H stretching of methyl group), 3030cm^{-1}(aromatic C-H stretching).

NMR:2.4δ(6*H*,singlet,two$-CH_3$),7.0-9.2δ(9*H*,multiplet,aromatic protons).

Compound 3g

IR: ν_{max}1715 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610$cm^{-1}$and 1430cm^{-1}(C=C and C=N stretching), 1235cm^{-1} (C-O-C stretching), 2930cm^{-1}(aliphatic C-H stretching of methyl group), 3030cm^{-1}(aromaticC-H stretching).

NMR:2.5δ(3*H*,singlet,$-CH_3$),3.9δ(3*H*,singlet,$-OCH_3$),7.0-9.2δ(9H, multiplet, aromatic protons).

Compound 3h

IR: ν_{max}1715 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1615$cm^{-1}$and 1445cm^{-1}(C=C and C=N stretching), 2935cm^{-1}(aliphatic C-H stretching of methyl group), 3035cm^{-1}(aromatic C-H stretching).

NMR: 2.5δ (3*H*, singlet, $-CH_3$), 7.0-9.2δ (9*H*, multiplet, aromatic protons).

Compound 3i

IR: ν_{max}1725 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1605$cm^{-1}$and 1440cm^{-1}(C=C and C=N stretching), 2940cm^{-1}(aliphatic C-H stretching of methyl group), 3035cm^{-1}(aromatic C-H stretching).

NMR:2.4δ(3*H*, singlet,-CH_3),7.1-9.0δ (10*H*, multiplet, aromatic protons).

Compound 3j

IR: ν $_{max}$1710 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1605cm^{-1} and 1430cm^{-1}(C=C and C=N stretching), 2950cm^{-1} (aliphatic C-H stretching of methyl group), 3050cm^{-1}(aromatic C-H stretching).

NMR:2.5δ(6*H*,singlet,two-CH_3),7.0-9.2δ (9*H*, multiplet, aromatic protons).

Compound 3k

IR: ν$_{max}$1710 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1} and 1430cm^{-1}(C=C and C=N stretching), 1250cm^{-1}(C-O-C stretching), 2940cm^{-1}(aliphatic C-H stretching of methyl group), 3030cm^{-1}(aromatic C-H stretching).

NMR:2.5δ(3*H*,singlet,-CH_3),3.9δ(3H,singlet,-OCH_3),6.9-8.8δ(9H, multiplet, aromatic protons).

Compound 3l

IR: ν$_{max}$1725cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1600cm^{-1}and 1435cm^{-1}(C=C and C=N stretching), 2950cm^{-1}(aliphatic C-H stretching of methyl group), 3030cm^{-1}(aromatic C-H stretching).

NMR: 2.5δ (3*H*, singlet, -CH_3), 7.2-9.2δ (9*H*, multiplet, aromatic protons).

Compound 3m

IR: ν $_{max}$ 1720 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1615cm^{-1}

and 1435cm^{-1}(C=C and C=N stretching),3035cm^{-1}(aromatic C-H stretching).

NMR:7.2-9.0δ (10*H*, multiplet, aromatic protons).

Compound 3n

IR: ν$_{max}$1710cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1}and 1445cm^{-1}(C=C and C=N stretching), 2935cm^{-1}(aliphatic C-H stretching of methyl group), 3055cm^{-1}(aromatic C-H stretching).

NMR: 2.5δ (3*H*, singlet, -CH_3), 7.0-9.0δ (9*H*, multiplet, aromatic protons).

Compound 3o

IR: ν$_{max}$1710cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1610cm^{-1} and 1430cm^{-1}(C=C and C=N stretching), 1245cm^{-1} (C-O-C stretching), 3050cm^{-1}(aromatic C-H stretching).

NMR:3.8δ(3*H*, singlet, -OCH_3), 6.8-8.9δ (9*H*, multiplet, aromatic protons).

Compound 3p

IR: ν$_{max}$1715 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1615cm^{-1}

and 1425cm^{-1}(C=C and C=Nstretching),3055cm^{-1}(aromatic C-H stretching).

NMR: 7.0-9.2δ (9H, multiplet, aromatic protons).

CONCLUSION

This series deals with synthesis of various 2-aryl-pyrido [3,2-*c*] coumarins. The compounds have been synthesized by reacting Mannich bases of various 4-hydroxy coumarins with pyridinium salts of various aroyl methyl bromides in the presence of ammonium acetate and acetic acid.

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