Available online on 15.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Case Report

Synthesis of furano[2,3-*c*] /pyrrolo[2,3-*c*]coumarins and synthesis of 1*(H)*-[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] furan-7*(H)*-ones /1*(H)*-[1]benzopyrano[3,4-*b*][1]benzopyrano [3',4'-*d*]pyrrole-7*(H)*-ones

Mahesh K. Pandya, Mehulsinh R. Chhasatia, Nileshkumar D. Vala, Tapan H. Parekh

Department of Chemistry Sardar Patel University,Vallabh Vidyanagar, Gujarat, (INDIA).

ABSTRACT

A series of synthesis of various 1-aryl-furano[2,3-*c*] and 1-phenyl-2-methyl-furano [2,3-*c*]coumarins;1-aryl-pyrrolo[2,3-*c*]and1-phenyl-2methylpyrrolo[2,3*c*]coumarins; 1aryl1*H*1] benzopyrano[3,4,-*b*][1]benzpyrano [3',4'-*d*]furan-7*H*-ones and 1-aryl-1*(H)*-[1]benzopyrano[3,4,-*b*][1]benzpyrano[3',4'-*d*]pyrrole-7*(H)*-ones. 1-Aryl-furano [2,3-*c*]coumarins and 1-phenyl-2-methyl-furano[2,3-*c*]coumarin have been synthesized by reacting 3-hydroxy coumarin with various 2-aryl-1-nitro-ethenes and 1-phenyl-2-nitro-propene respectively in the presence of piperidine and methanol as solvent. 1-Aryl-pyrrolo [2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo[2,3-*c*] coumarin also have been synthesised by reacting 3-amino coumarin with various 2-aryl-1-nitro-ethenes and 1-phenyl-2-nitro-propene respectively in the presence of piperidine and methanol. The formation of furan and pyrrole nucleus in all above compounds follows Nef reaction mechanism. Using the Nef reaction, synthesis of various 1-aryl-1*(H)*-[1]benzopyrano[3,4,-*b*][1]benzpyrano[3',4'-*d*]furan-7*(H)*-ones have been carried out by reacting various 4-hydroxy coumarins with various 3-nitro-2-aryl-2*H*-[1]benzopyrans in the presence of piperidine and methanol. Similarly synthesis of various 1-aryl-1*(H)*-[1]benzopyrano[3,4,-*b*][1]benzpyrano [3',4'-*d*]pyrrole-7*(H)*-ones also have been carried out by reacting various 4-hydroxy coumarins with various 3-nitro-2-aryl-2H-[1]benzopyrans in the presence of ammoniun acetate and acetic acid.

Keywords: Furan, Pyrrolo,Coumarin, Benzopyrano.

Article Info: Received 13 June 2019; Review Completed 19 July 2019; Accepted 22 July 2019; Available online 15 Aug 2019

Cite this article as:

Pandya MK, Chhasatia MR, Vala ND, Parekh TH, Synthesis of furano[2,3-*c*] /pyrrolo[2,3-*c*]coumarins and synthesis of 1*(H)*-[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] furan-7*(H)*-ones /1*(H)*-[1]benzopyrano[3,4-*b*][1]benzopyrano [3',4'-*d*]pyrrole-7*(H)*-ones, Journal of Drug Delivery and Therapeutics. 2019; 9(4):32-42

http://dx.doi.org/10.22270/jddt.v9i4.3243

***Address for Correspondence:**

Mehulsinh R. Chhasatia, Department of Chemistry Sardar Patel University,Vallabh Vidyanagar, Gujarat, (INDIA).

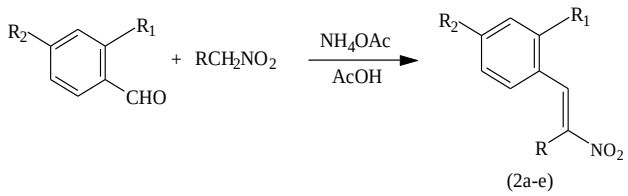
1. Introduction

A series comprises synthesis of various 1-aryl-furano[2,3-*c*] and 1-phenyl-2-methyl-furano[2,3-*c*]coumarin; 1-aryl-pyrrolo[2,3-*c*] and 1-phenyl-2-methyl-pyrrolo[2,3-*c*] coumarin; 1-phenyl-1*(H)*-[1] benzopyrano[3,4,-*b*][1] benzpyrano [3',4'-*d*]furan-7*(H)*-ones and 1-phenyl-1*(H)*-[1]benzopyrano[3,4,-*b*][1]benzopyrano [3',4'-*d*] pyrrole-7*(H)*-ones.1-Aryl-furano[2,3-*c*]coumarins and 1-phenyl-2-methyl-furano[2,3-*c*] coumarin have been synthesized by reacting 3-hydroxy coumarin with various 2-aryl-1-nitro ethenes and 1-phenyl -2-nitro-propene respectively in the presence of piperidine and methanol as solvent. 1-Aryl-pyrrolo[2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo[2,3-*c*] coumarin have been synthesized by reacting 3-amino coumarin with various 2-aryl-1-nitro-ethenes and 1-phenyl-2-nitro-propene respectively in the presence of piperidine and methanol. The formation of furan and pyrrole nucleus in all above compounds follows Nef reaction mechanism [1-3]. Using the Nef reaction, synthesis of various 1-aryl-1*(H)*-[1]benzopyrano[3,4,-*b*][1] benzpyrano[3',4'-*d*]furan-7*(H)*-ones have also been carried out by reacting various 4-hydroxy coumarins with various 3-nitro-2-aryl-2*H*-[1]benzopyrans in the presence of piperidine and methanol[4]. Similarly synthesis of various 1-aryl-1*(H)*-[1]benzopyrano[3,4,-*b*][1] benzpyrano [3',4'-*d*]pyrrole-7*(H)*-ones have also been carried out by reacting various 4-hydroxy coumarins and various 3-nitro-2-aryl-2*H*-[1]benzopyrans in the presence of ammonium acetate and acetic acid. All the compounds synthesized have been characterized by analytical and spectral data

2. Experimental

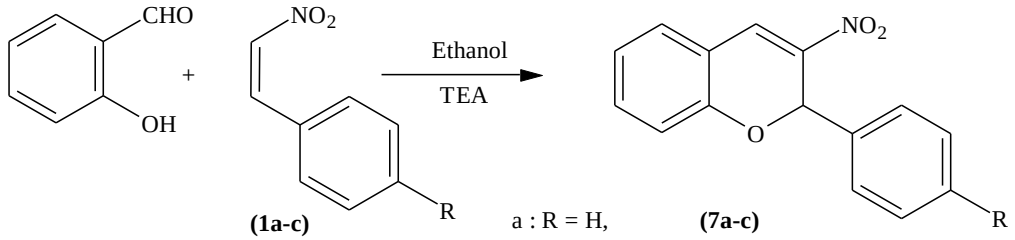
2.1 Preparation of 2-aryl-1-nitro-ethenes / 1-phenyl-2-nitro-propene (2a-e).

Substituted aldehydes (0.16 mole), appropriate nitro alkane (0.1 mole), ammonium acetate (0.16 mole) and glacial acetic acid (100 ml) were mixed in a 250 ml round bottom flask fitted with a reflux condenser. The reaction mixture was refluxed for 4 to 5 hours in an oil bath. It was then poured into crushed ice. Fine yellow crystals irritating to the skin obtained were filtered out and were recrystallised from rectified spirit. [5,6]



(2a-e)

2.2 Preparation of 3-nitro-2-aryl-2*H*-[1] benzopyrans (7a-c).



(1a-c) **(7a-c)**

a : R = H,
b : R = -CH_3,
c : R = -OCH_3

In a 100 ml round bottom flask fitted with reflux condenser, a mixture of salicylaldehyde (0.01mol), 2-aryl-1-nitro-ethenes (0.005 mole**)** and triethylamine (0.002 mole) was taken in ethanol (30 ml). Then reaction mixture was refluxed for 5 hours. Then the solvent was removed under reduced pressure. The solid product obtained was filtered out and washed with water and recrystllized from eathanol.

2.3 Preparation of 3-hydroxy coumarin (1).

The 3-hydroxy coumarin was synthesized in two steps.

Step:1 Preparation of 2-phenyl -4-(2'-acetoxybenzal) oxazolone.

In a 500 ml three necked round bottom flask euipped with reflux condenser and guard tube, a mixture of salicylaldehyde (25 g, 0.2 mole), hippuric acid (42 g., 0.278 mole), fused sodium acetate (15 g.) and acetic anhydride (60 ml) was taken. The reaction mixture was then heated in a boiling water bath for 30 minutes. On cooling the reaction mixture to room temperature, a bright yellow crystalline solid product was formed. Ethanol (20 ml) was then added and the reaction mixture was further heated for 10 minutes in water bath, during which the above solid was redissolved. The reaction mixture was then kept at room temperature for 6 hours and the separated 2**-**phenyl-4-(2'-acetoxybenzal) oxazolone was filtered out. It was then washed with cold ethanol and hot water. It was recrystallized from ethanol. Yield, 40g.(63.6%).[7-12]

Step:2 3-Hydroxy coumarin.

In a 500 ml three necked round bottom flask equipped with reflux condenser, was put above prepared 2-phenyl-4-(2'-acetoxybenzal) oxazolone (40g.). To this 20% NaOH solution (100 ml) was added slowly. It was then heated in boiling water bath for 2 hours. Then after the reaction mixture was diluted with water (100 ml) and allowed to come to room temperature. Then sulfur dioxide gas was passed through the reaction mixture under cold condition till it became saturated. The reaction mixture was left for 12 hours and the separated benzoic acid was filtered out. To the filtrate, 60 ml concentrated hydrochloric acid was added and it was heated in boiling water bath for 2 hours. On cooling, 3-hydroxy coumarin was separated out which was filtered out, washed with cold water and recrystallized from ethanol. Yield, 13g, (61%); m.p.: 151-52°C [7-12]

2.4 Preparation of 3-amino coumarin (4).

The 3-amino coumarin was synthesized in two steps.

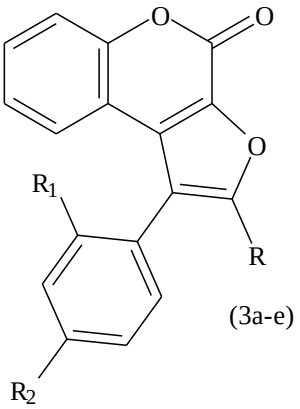
Step:1 Preparation of 3-acetylamino coumarin.

In a 500 ml round bottom flask equipped with reflux condenser and guard tube, a mixture of glycine (25.0 g. 0.32 mole), salicylaldehyde (40.0 g., 0.32 mole), fused sodium acetate (35.0 g.) and acetic anhydride (100 ml) were mixed together and the reaction mixture was heated in an oil bath at 120°C for 6 hours. Initially the reaction mixture became yellow liquid and then it was darkened considerably during the heating. It was allowed to come to room temperature and left overnight. On next day, it was solidified. The solid product was taken out and washed with chilled ethanol and then with hot water. The 3-acetylamino coumarin was obtained as yellow crystalline solid. Yield, 55%, m.p.: 199°C

Step:2 3-Amino coumarin.

In a 500 ml three necked round bottom flask equipped with reflux condenser, above prepared 3-acetylamino coumarin was taken and it was dissolved in 50% hydrochloric acid solution (150 ml). It was then boiled for 3 hours. Then the acid solution was neutralized with sodium carbonate, whereby 3-aminocoumarin was obtained as a solid product. It was filtered out, washed with water and dried. It was recrystallized from ethanol. Yield, 65%. m.p.: 128-29°C .

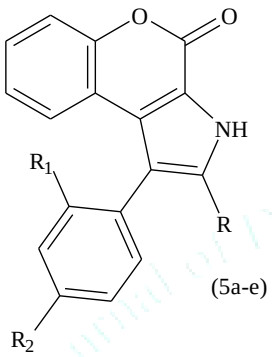
2.5 Synthesis of 1-aryl-furano [2,3-*c*] coumarins and 1-phenyl-2-methyl- furano[2,3-*c*] coumarin (3a-e).



(3a-e)

A mixture of 3-hydroxy coumarin (0.006 mole) and an appropriate 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (0.006 mole) and methanol (40 ml) were taken in 100 ml round bottom flask. To this piperidine (0.006 mole) was added at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 6 hours in oil bath. Then after the solvent was removed under reduced pressure. The residue was treated with water (100 ml) and was extracted with chloroform (3x30 ml). The chloroform extract was successfully washed with dil.HCl and water. It was then dried over anhydrous sodium sulphate. The removal of solvent gave gummy residue, which was subjected to column chromatography using silica gel and chloroform-pet.ether (60:80) (4:6) as an eluent to give compounds (3a-e). The compounds thus obtained were recrystallised from chloroform-hexane.

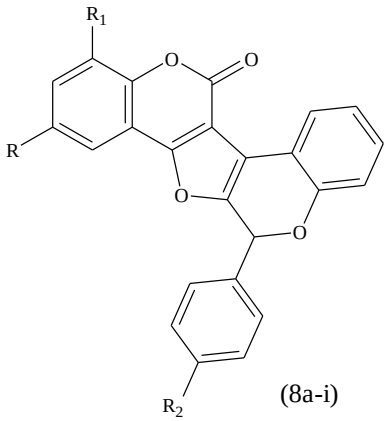
2.6 Synthesis of 1-aryl-pyrrolo [2,3-*c*]coumarins and 1-phenyl- 2-methyl- pyrrolo[2,3-*c*] coumarin (5a-e).



(5a-e)

A mixture of 3-amino coumarin (0.006 mole) and appropriate 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (0.006 mole) and methanol (40 ml) were taken in 100 ml round bottom flask. To this piperidine (0.006 mole) was added at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 6 hours in oil bath. Then after the solvent was removed under reduced pressure. The residue was treated with water (100 ml) and was extracted with chloroform (3x30 ml). The chloroform extract was washed with water. It was then dried over anhydrous sodium sulphate. The removal of solvent gave gummy residue, which was subjected to column chromatography using silica gel and ethyl acetate-pet.ether (60:80) (4:6) as an eluent to give compounds (5a-e). The compounds thus obtained were recrystallised from chloroform-hexane.

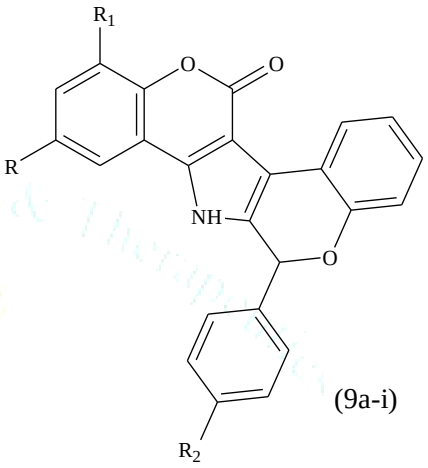
2.7 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] furan-7*(H)*-ones (8a-i).



(8a-i)

A mixture of appropriate 4-hydroxy coumarin (0.006 mole) and appropriate 3-nitro-2-aryl-2*H*-[1]benzopyran (0.006 mole) and methanol (50 ml) were taken in 100 ml round bottom flask. To this piperidine (0.006 mole) was added at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 6 hours in oil bath. Then after the solvent was removed under reduced pressure. The residue was treated with water (50 ml) and was extracted with chloroform (3x30 ml). The chloroform extract was successfully washed with dil.HCl and water. It was then dried over anhydrous sodium sulphate. Then after the removal of solvent gave gummy residue, which was subjected to column chromatography using silica gel and chloroform-pet.ether (60-80) (6:4) as an eluent to give compounds (8a-i). The compounds thus obtained were recrystallised from chloroform-hexane.

2.8 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1] benzopyrano[3',4'-*d*] pyrrole-7*(H)*-ones (9a-i).

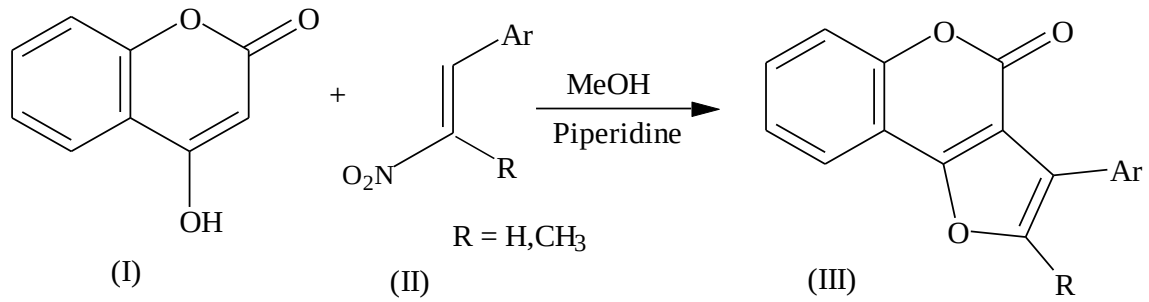


(9a-i)

A mixture of appropriate 4-hydroxy coumarin (0.006 mole) and ammonium acetate (0.06 mole) in acetic acid were taken in 100 ml round bottom flask. To this appropriate 3-nitro-2-aryl-2*H*-[1]benzopyran (0.006 mole) in acetic acid (15 ml) was added at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 13 hours at 140°C in oil bath. It was then allowed to come to room temperature and was poured into ice-cold water (100 ml). A sticky mass was separated out which was then extracted with chloroform (3x30 ml). The chloroform layer was then washed with 5% $NaHCO_3$ and then with water. It was then dried over anhydrous sodium sulphate. Then after the chloroform was removed under reduced pressure. The gummy residue obtained, which was subjected to column chromatography using silica gel and ethyl acetate-pet.ether (60-80) (3:7) as an eluent to give compounds (9a-i). The compounds thus obtained were recrystallised from chloroform-hexane.

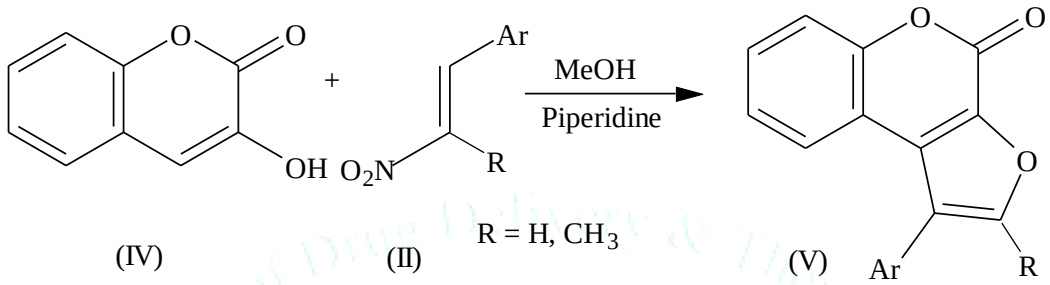
3.1 Synthesis

Considering the importance of the furano coumarins and with a view to developing new method for the synthesis of furano coumarins earlier [13] one method was developed from our laboratory and synthesis of some furano [3,2-*c*]coumarins was carried out. The work is out lined below.

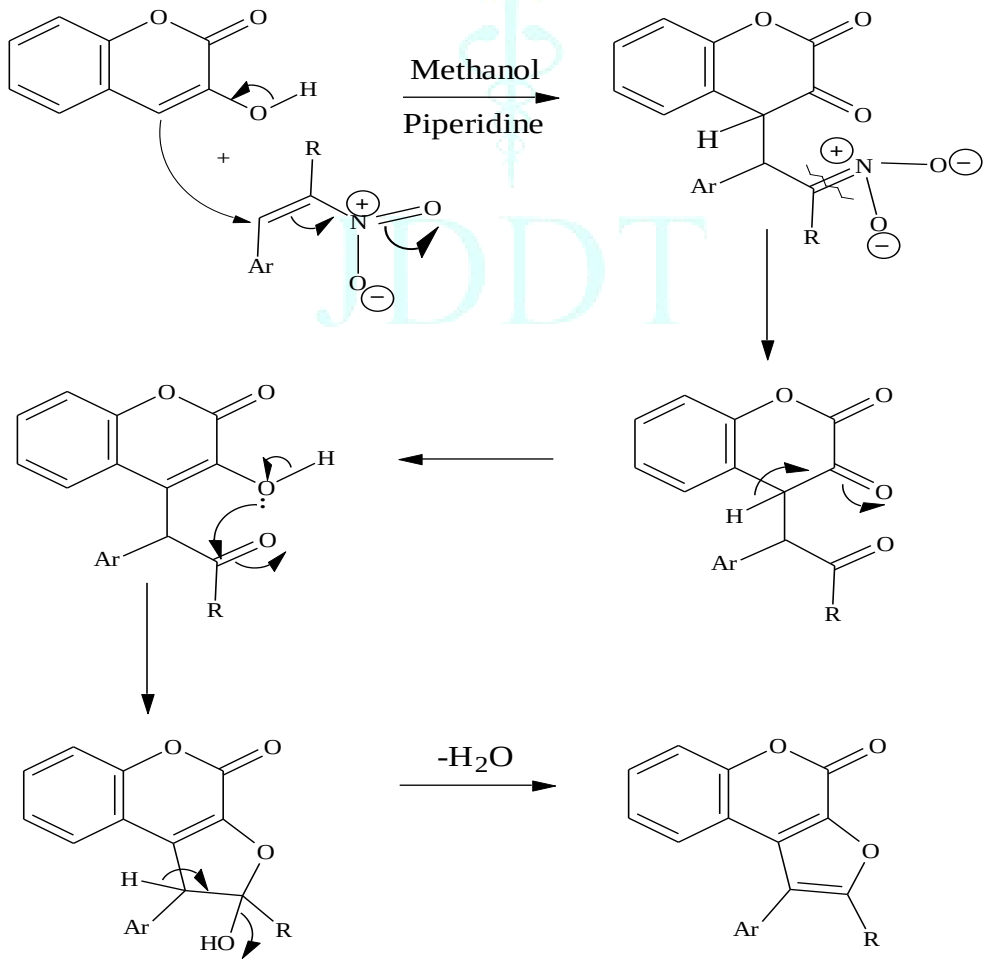


Thus 4-hydroxy coumarin (I) upon reaction with 2-aryl-1-nitro ethenes (II) under Nef reaction condition gave furano[3,2-*c*]coumarins (III).

Now in the present work the same methodology is applied on 3-hydroxy coumarin and various furano [2,3-*c*] coumarins have been synthesized. The synthetic scheme is shown below.



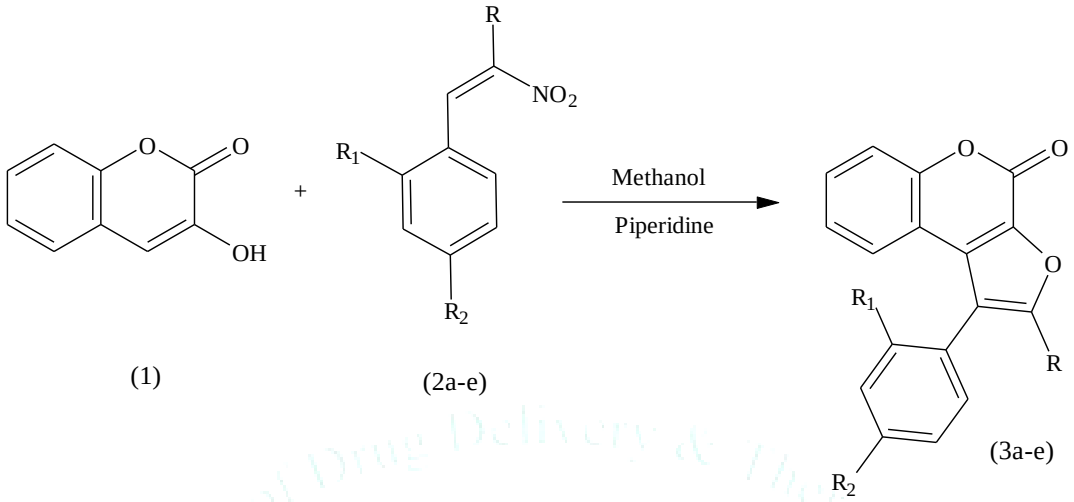
Thus reaction of 3-hydroxy coumarin (IV) with 2-aryl-1-nitro-ethenes/1-phenyl-2-nitro-propene (II) under Nef reaction condition can give furano [2,3-*c*] coumarins (V). The mechanism for the reaction is shown below.



Thus 3-hydroxy coumarin was reacted with various 2-aryl-1-nitro ethenes /1-phenyl-2-nitro-propene under Nef reaction condition and various 1-aryl-furano [2,3-*c*] coumarins and 1-phenyl-2-methyl- furano[2,3-*c*]coumarin have been synthesized.

3.2 Synthesis of 1-aryl-furano[2,3-*c*]coumarins and 1-phenyl-2-methyl- furano[2,3-*c*]coumarin (3a-e) (Scheme-1).[14]

The synthesis of 1-aryl-furano[2,3-*c*]coumarins and 1-phenyl-2-methyl-furano [2,3-*c*]coumarin (3a-e) have been carried out by reacting 3-hydroxy coumarin (1) with appropriate 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (2a-e) in the presence of piperidine using methanol as a solvent under Nef reaction condition.



(1) (2a-e) (3a-e)

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= OCH_3, R_2 = OCH_3
e : R = CH_3, R_1= H, R_2 = H

(Scheme-1)

The condensation of 3-hydroxy coumarin (1) with 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (2a-e) in the presence of methanol and piperidine under Nef reaction condition proceeded smoothly and gave the expected 1-aryl-furano[2,3-*c*] coumarins / 1-phenyl-2-methyl-furano[2,3-*c*]coumarin (3a-e) in 55-61 % yield. The structures of all the compounds (3a-e) were confirmed by analytical and spectral data.

All compounds in their IR spectra showed a charactristic coumarin carbonyl stretching band between 1715-1725 cm^{-1}. Compounds showed a band around 1120 cm^{-1} due to C-O-C stretching of furan moiety. Compounds also showed bands around 1610cm^{-1} and 3040cm^{-1} for aromatic C=C and aromatic C-H stretchings respectively. All compounds gave satisfactory NMR spectra (60MHz). The spectral data are listed below.

Compound 3a

IR: λ_{max}1720 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1110cm^{-1}(furan C-O-C-stretching), 1605cm^{-1} (aromatic C=C stretching), 3045cm^{-1} (aromatic C-H stretching).NMR, 7.0-8.4δ (10*H*, multiplet, aromatic protons including furan proton).

Compound 3b

IR: λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1120cm^{-1}(furanC-O-C-stretching), 1600cm^{-1} (aromatic C=C stretching), 2942cm^{-1} (aliphatic C-H stretching of methyl group), 3035cm^{-1}(aromatic C-H stretching).NMR, 2.3δ (3*H*, singlet, -CH_3), 6.8-8.4δ (9*H*, multiplet, aromatic protons including furan proton).

Compound 3c

IR: λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1115cm^{-1} (furanC-O-stretching), 1615cm^{-1} (aromatic C=C stretching), 3040cm^{-1}(aromatic C-H stretching).NMR, 3.8δ (3*H*, singlet, -OCH_3), 6.7-8.4δ (9*H*, multiplet, aromatic protons including furan proton).

Compound 3d

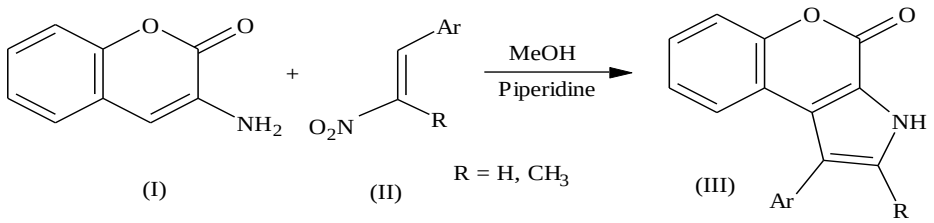
IR: λ_{max}1720cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1125cm^{-1}(furan C-O-C-stretching), 1610cm^{-1} (aromatic C=Cstretching), 3055cm^{-1}(aromatic C-H stretching).NMR, 3.8δ (6*H*, singlet, two-OCH_3), 6.9-8.4δ (8*H*, multiplet, aromatic protons including furan proton)

Compound 3e

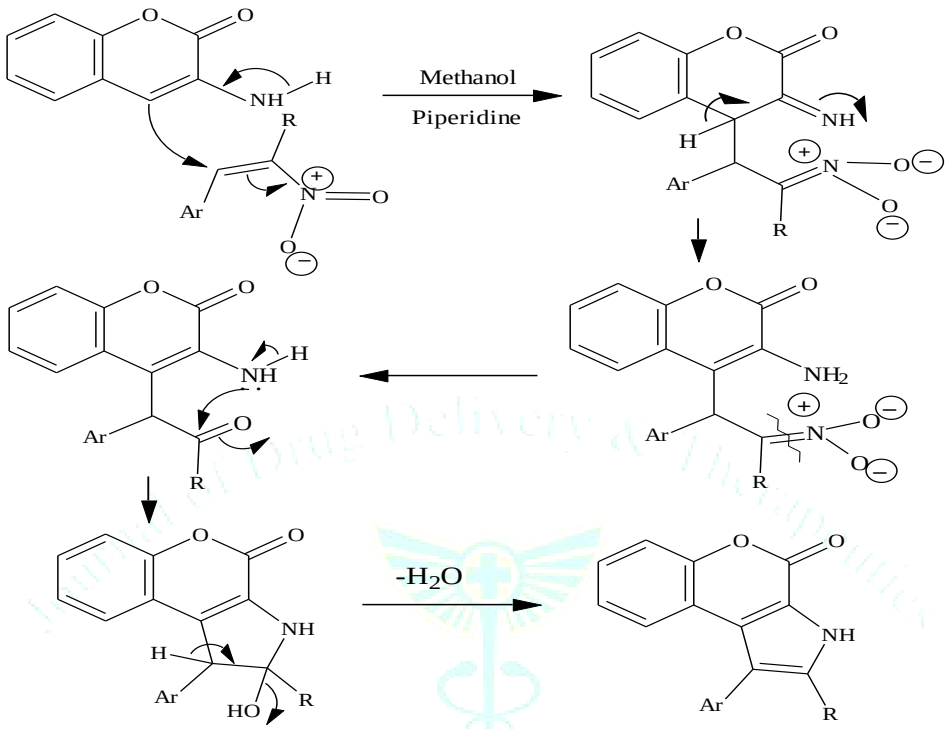
IR: λ_{max}1725cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1120cm^{-1}(furan C-O-C-stretching), 1605cm^{-1} (aromatic C=C stretching), 2935cm^{-1} (aliphatic C-H stretching of methyl group), 3030cm^{-1}(aromatic C-H stretching). NMR, 2.4δ (3*H*, singlet,-CH_3), 6.9-8.1δ (9*H*, multiplet, aromatic protons).

3.3 Synthesis of pyrrolo[2,3-*c*]coumarins

The success of synthesis of various furano[2,3-*c*]coumarins prompted author to extend this methodology to synthesize pyrrolo[2,3-*c*]coumarins. Thus if 3-amino coumarin (I) is reacted with 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (II) in the presence of piperidine using methanol as a solvent under Nef reaction condition then it can give 1-aryl-pyrrolo[2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo [2,3-*c*] coumarin (III) as shown below.



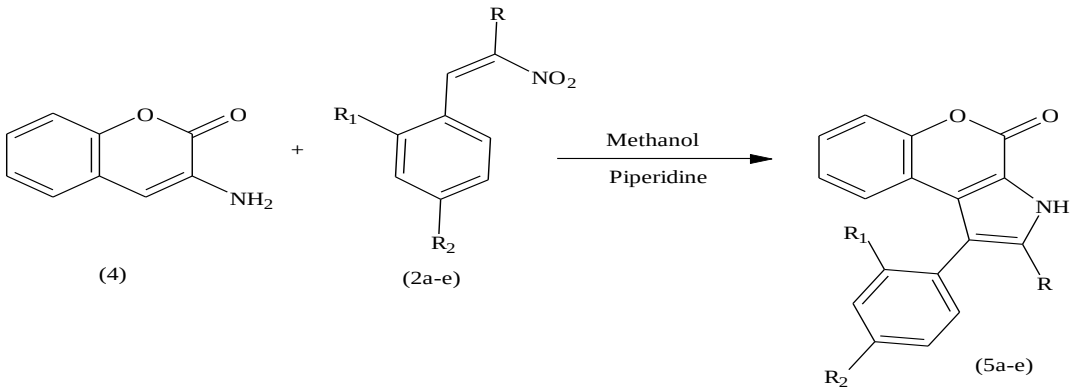
The mechanism for the formation of (III) can be shown below.



Thus 3-aminocoumarin was reacted with various 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene under Nef reaction condition and various 1-aryl-pyrrolo[2,3-*c*] coumarins and 1-phenyl-2-methyl- pyrrolo[2,3-*c*]coumarin have been synthesize[15]

The synthesis of 1-aryl-pyrrolo[2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo [2,3-*c*]coumarin (5a-e) have been carried out by reacting 3-aminocoumarin (4) with appropriate 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (2a-e) in the presence of piperidine using methanol as a solvent under the Nef reaction condition. [16]

3.4 Synthesis of 1-aryl-pyrrolo [2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo [2,3-*c*]coumarin (5a-e) (Scheme-2).



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= OCH_3, R_2 = OCH_3
e : R = CH_3, R_1= H, R_2 = H

(Scheme-2)

The condensation of 3-aminocoumarin (4) with 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (2a-e) in the presence of methanol and piperidine under Nef reaction condition proceeded smoothly and gave the expected 1-aryl-pyrrolo[2,3-*c*] coumarins / 1-pheyl-2-methyl-pyrrolo[2,3-*c*]coumarin (5a-e) in 51-57 % yield. The structures of all the compounds (5a-e) were confirmed by analytical and spectral data.All the compounds in their IR spectra showed a charactristic coumarin carbonyl stretching band between 1705-1720 cm^{-1}. Compounds showed a band between 3350-3370 cm^{-1}due to N-H stretching of pyrrole moiety. Compounds also showed bands around 1615cm^{-1} and 3030cm^{-1} for aromatic C=C and aromatic C-H stretchings respectively. All the compounds gave satisfactory NMR spectra (60MHz). Here it is important to mention that in the NMR spectrum of all the compounds, the signal for N-H proton was merged with the aromatic protons signal. This was confirmed by scanning the spectra after D_2O exchanged and observing the integration for the signal in the aromatic region which decreased in value for one proton.

Compound 5a

IR: λ_{max} 1705 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3365cm^{-1}(N-H stretching), 1605cm^{-1} (aromatic C=C stretching), 3045cm^{-1} (aromatic C-H stretching).NMR, 7.0-8.6δ (11*H*, multiplet, 10 aromatic protons including C_1H + -NH proton merged).

Compound 5b

IR: λ_{max}1715 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3355 cm^{-1}(N-H stretching), 1610cm^{-1} (aromatic C=C stretching), 2955 cm^{-1} (aliphatic C-H stretching of methyl group), 3035cm^{-1} (aromatic C-H stretching).NMR, 2.3δ (3*H*, singlet, -CH_3), 6.8-8.5δ (10*H*, multiplet, 9 aromatic protons including C_1H + -NH proton merged).

Compound 5c

IR: λ_{max}1710 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3360cm^{-1}(N-H stretching), 1615cm^{-1} (aromatic C=C stretching), 3030cm^{-1}(aromatic C-H stretching).NMR, 3.8δ (3*H*, singlet, -OCH_3), 6.8-8.5δ (10*H*, multiplet, 9 aromatic protons including C_1H + -NH proton merged).

Compound 5d

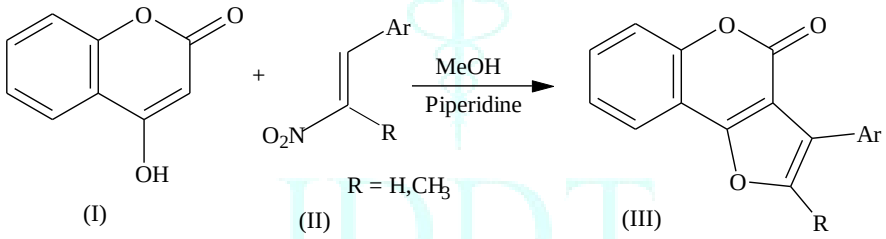
IR: λ_{max}1705cm^{-1}(δ-lactone carbonyl stretching of coumarin),3370cm^{-1} (N-H stretching), 1605cm^{-1} (aromatic C=C stretching), 3040cm^{-1}(aromatic C-H stretching).NMR , 3.8δ (6*H*, singlet, two-OCH_3), 6.9-8.4δ (9*H*, multiplet, 8 aromatic Protons including C_1H + -NH proton merged).

Compound 5e

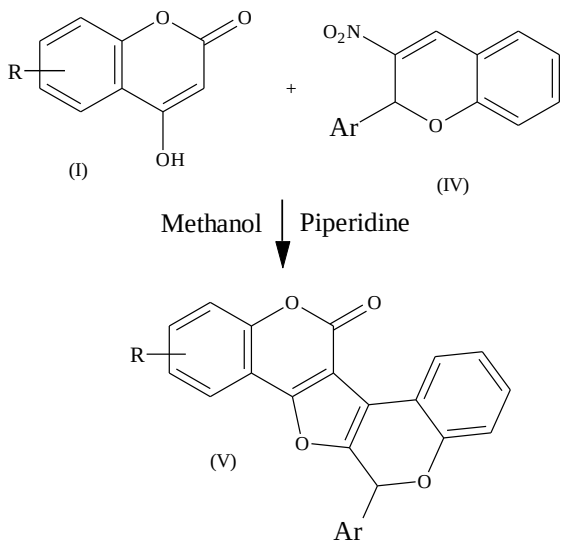
IR: λ_{max}1720 cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3350cm^{-1} (N-H stretching), 1610cm^{-1} (aromatic C=C stretching), 2940cm^{-1} (aliphatic stretching of methyl group), 3035cm^{-1}(aromatic C-H stretching).NMR, 2.4δ(3*H*, singlet, -CH_3), 6.9-8.5δ (10*H*, multiplet, 9 aromatic protons + -NH proton merged).

3.5 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1] benzopyrano[3',4'-*d*] furan-7*(H)*-ones.

The reaction of 4-hydroxy coumarin (I) with 2-aryl-1-nitro-ethenes (II) under Nef reaction condition gives furano[3,2-*c*]coumarins (III). [13]



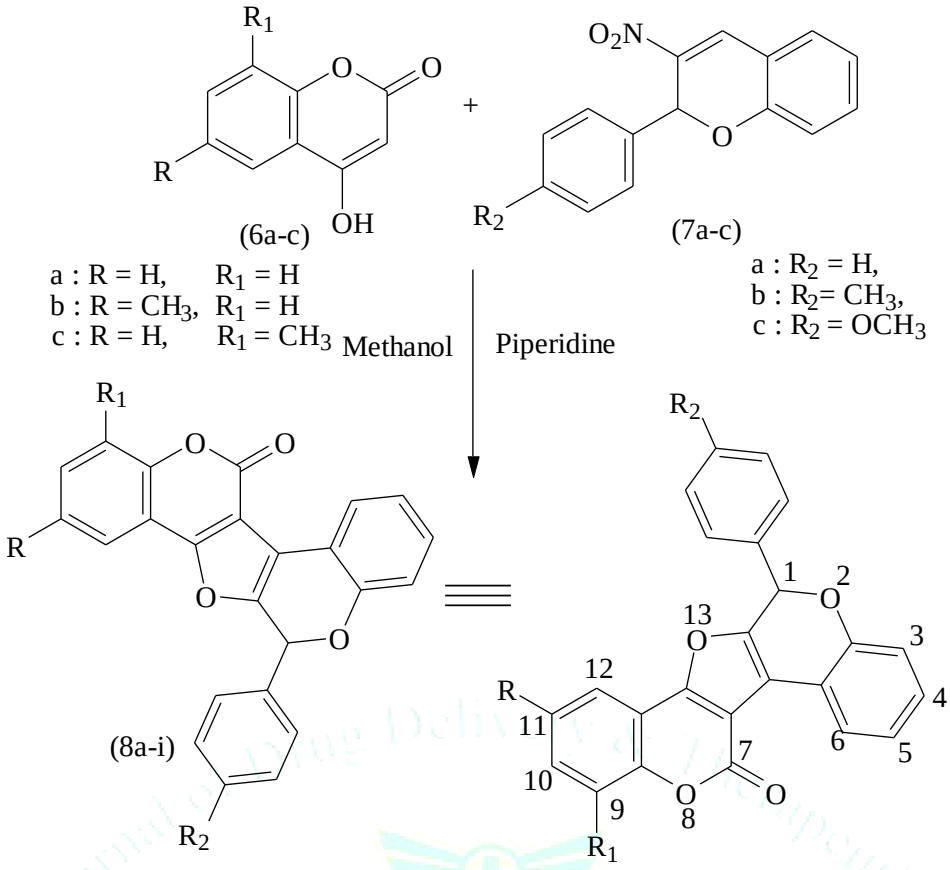
Now if instead of 2-aryl-1-nitro-ethenes (II), 3-nitro-2-aryl-2*H*-[1] benzopyran (IV) is reacted with 4-hydroxy coumarin (I), then it can give a novel furano fused coumarin derivative i.e. 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*]furan-7*(H)*-one (V) as shown below.



Here as the component (IV) is having 2-aryl-1-nitro-ethene (cyclic) analogous structure, it can undergo Nef reaction similar to 2-aryl-1-nitro-ethene following the parallel mechanism. Thus keeping this concept in mind, reaction of various 4-hydroxy coumarins with 3-nitro-2-aryl-2*H*-[1] benzopyrans have been carried under Nef reaction condition and various 1-aryl-1*H*[1]benzopyrano[3,4-*b*] [1]benzopyrano[3',4'-*d*]furan-7*(H)*-ones have been synthesized.

3.6 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1] benzopyrano [3',4'-*d*] furan-7*(H)*-ones (8a-i) (Scheme-3).

The synthesis of 1-aryl-1H[1]benzopyrano[3,4-*b*][1] benzopyrano [3',4'-*d*] furan-7*(H)*-ones (8a-i) have been carried out by reacting various 4-hydroxy coumarins (6a-c) with appropriate 3-nitro-2-aryl-2*H*-[1]benzopyrans (7a-c) in the presence of piperidine using methanol as a solvent under Nef reaction condition.



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= CH_3, R_1= H, R_2= H
e ; R= CH_3, R_1= H, R_2= CH_3
f ; R= CH_3, R_1= H, R_2= OCH_3
g ; R= H, R_1= CH_3, R_2= H
h ; R= H, R_1= CH_3, R_2= CH_3
i ; R= H, R_1= CH_3, R_2= OCH_3

(Scheme-3)

The condensation of 4-hydroxy-coumarins (6a-c) with appropriate 3-nitro-2-aryl-2*H*-[1]benzopyrans (7a-c) in the presence of piperidine using methanol as a solvent under Nef reaction condition proceeded smoothly and gave the expected 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano [3',4'-*d*] furan-7*(H)*-ones (8a-i) in 54 -59 % yield. The structures of all the compounds (8a-i) were confirmed by analytical and spectral data.All the compounds in their IR spectra showed a characristic coumarin carbonyl stretching band between 1700-1720cm^{-1}. Compounds showed a band around 1125cm^{-1} due to C-O-C stretching of furan moiety. Compounds also showed bands around 1610cm^{-1} and 3045cm^{-1} for aromatic C=C and aromatic C-H stretchings respectively. All the compounds gave satisfactory NMR spectra (60MHz). Here it is important to mention that in the NMR spectrum of all the compounds, the methine proton (C_1-H) was merged with aromatic protons signals. The spectral data are listed below.

Compound 8a

IR:λ_{max}1705cm^{-1}(δ-lactone carbonyl stretching of coumarin),1120cm^{-1}(furan C-O-C stretching),1610cm^{-1} (aromatic C=C stretching), 3030cm^{-1}(aromatic C-H stretching).NMR: 6.2-8.9δ (14*H*, multiplet, 13 aromatic protons + C_1-H)

Compound 8b

IR: λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1125cm^{-1}(furan C-O-C stretching), 1615m^{-1} (aromatic C=C stretching),2945cm^{-1}(aliphatic C-H stretching of methyl group), 3040cm^{-1}(aromatic C-H stretching).NMR, 2.3δ (3*H*, singlet, -CH_3), 6.2-8.9δ (13*H*, multiplet, 12 aromatic protons+ C_1-H).

Compound 8c

IR: λ_{max}1700cm^{-1}(δ-lactone carbonyl stretching of coumarin),1130cm^{-1} (furan C-O-C stretching), 1605cm^{-1} (aromatic C=C stretching),3040cm^{-1} (aromatic C-H stretching).NMR, 3.8δ (3*H*, singlet, -OCH_3), 6.3-9.0δ (13*H*, multiplet, 12 aromatic protons + C_1-H).

Compound 8d

IR: λ_{max}1720cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1115cm^{-1} (furan C-O-C stretching),1600cm^{-1} (aromatic C=C stretching), 2950cm^{-1}(aliphatic C-H stretching of methyl group), 3030cm^{-1} (aromatic C-H stretching).NMR,

2.4δ (3*H*, singlet, –CH_3), 6.3-8.9δ (13*H*, multiplet, 12 aromatic protons + C_1-H).

Compound 8e

IR:λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin),1125cm^{-1}(furan C-O-C stretching),1610cm^{-1} (aromatic C=C stretching),2935cm^{-1} (aliphatic C-H stretching of methyl group), 3030cm^{-1} (aromatic C-H stretching).NMR,2.3δ (6*H*, singlet, two-CH_3), 6.0-8.9δ (12*H*, multiplet, 11 aromatic+ C_1-H).

Compound 8f

IR:λ_{max}1705cm^{-1}(δ-lactone carbonyl stretching of coumarin), 1120cm^{-1} (furan C-O-C stretching), 1600m^{-1} (aromatic C=C stretching), 2930cm^{-1}(aliphatic C-H stretching of methyl group), 3045cm^{-1}(aromatic C-H stretching).NMR, 2.3 δ(3*H*, singlet, -CH_3),3.8δ (3*H*, singlet, -OCH_3), 6.0-8.8δ(12*H*, multiplet, 11 aromatic protons + C_1-H).

Compound 8g

IR: λ_{max}1710cm^{-1}(δ-lactone carbonyl stretching of coumarin),1125cm^{-1}(furan C-O-C stretching),1605cm^{-1} (aromatic C=C stretching),2935cm^{-1} (aliphatic C-H stretching of methyl group), 3055cm^{-1} (aromatic C-H stretching).NMR, 2.4δ (3*H*, singlet, -CH_3), 6.2-8.9δ (13*H*, multiplet, 12 aromatic protons+ C_1-H).

Compound 8h

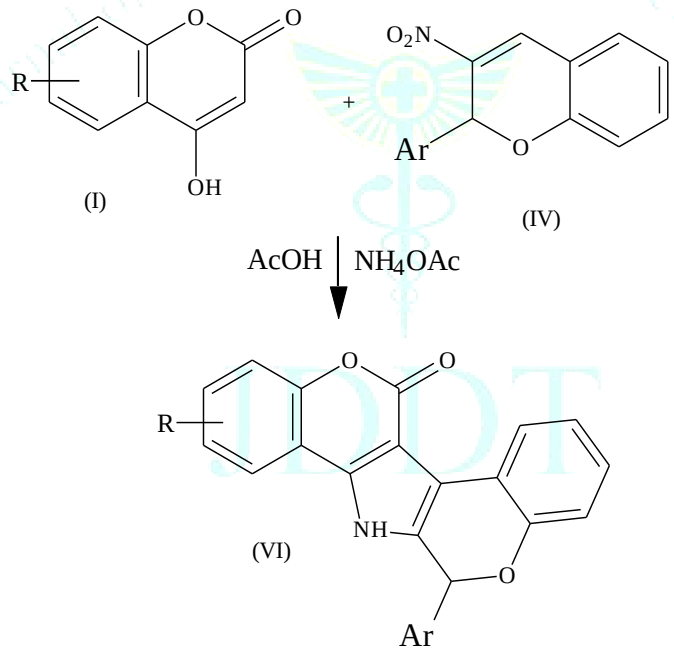
IR: λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin),1120cm^{-1}(furanC-O-C stretching), 1615cm^{-1} (aromatic C=C stretching), 2945cm^{-1} (aliphatic C-H stretching of methyl group), 3035cm^{-1} (aromatic C-H stretching).NMR, 2.4δ (6*H*, singlet, two -CH_3), 6.3-9.0δ (12*H*, multiplet, 11 aromatic protons + C_1-H).

Compound 8i

IR:λ_{max}1720cm^{-1}(δ-lactone carbonyl stretching of coumarin),1130cm^{-1}(furanC-O-C stretching),1610cm^{-1} (aromatic C=C stretching),2940cm^{-1}(aliphatic C-H stretching of methyl group), 3050cm^{-1} (aromatic C-H stretching).NMR, 2.3δ (3*H*, singlet, -CH_3), 3.8δ (3*H*, singlet,-OCH_3) 6.1-8.9δ (12*H*,multiplet, 11 aromatic protons + C_1-H).

3.7 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] pyrrole-7*(H)*-ones.[17]

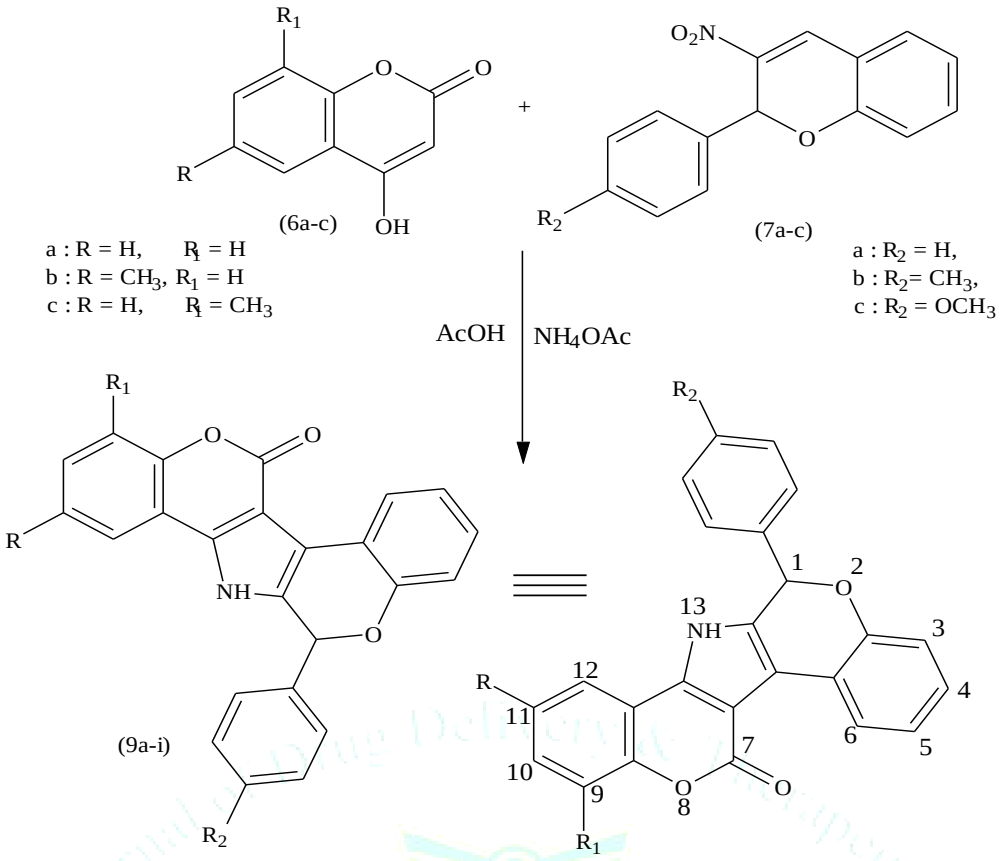
If the reaction of 4-hydroxy coumarin (I) is carried-out with 3-nitro-2-aryl-2*H*-[1]benzopyrans (IV) in the presence of ammonium acetate and acetic acid, it can give novel 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*]pyrrole-7*(H)*-ones(VI).



Here, in the presence of ammonium acetate and acetic acid, the 4-hydroxy coumarin (I) will be initially converted into corresponding 4-amino coumarin which will subsequently react with 3-nitro-2-aryl-2*H*-[1]benzo pyrans (IV) under Nef reaction condition and will give 1-aryl-1*H*[1] benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] pyrrole-7*(H)*-ones (VI) following the parallel mechanism .Thus in the present work above methodology has been implemented and the reaction of various 4-hydroxy coumarins (I) with appropriate 3-nitro-2-aryl-2*H*-[1]benzopyrans (IV) have been carried out in the presence of ammonium acetate and acetic acid to give various 1-aryl-1*H*[1]benzo- pyrano [3,4-*b*][1]benzopyrano [3',4'-*d*] pyrrole-7*(H)*-ones (VI).

3.8 Synthesis of 1-aryl-1*H*[1]benzopyrano[3,4-*b*][1]benzopyrano[3',4'-*d*] pyrrole-7*(H)*-ones (9a-i) (Scheme-4).

The synthesis of 1-aryl-1*H* [1] benzopyrano[3,4-*b*][1]benzopyrano [3',4'-*d*] pyrrole-7*(H)*-ones (9a-i) have been carried out by reacting various 4-hydroxy-coumarins (6a-c) with appropriate 3-nitro-2-aryl-2*H*-[1]benzopyrans (7a-c) in the presence of ammonium acetate and acetic acid.



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 = CH_3, R_1 = H, R_2 = H
e ; R = CH_3, R_1 = H, R_2 = CH_3
f ; R = CH_3, R_1 = H, R_2 = OCH_3
g ; R = H, R_1 = CH_3, R_2 = H
h ; R = H, R_1 = CH_3, R_2 = CH_3
i ; R = H, R_1 = CH_3, R_2 = OCH_3

(Scheme-4)

The condensation of 4-hydroxy coumarins (6a-c) with appropriate 3-nitro-2-aryl-2*H*-[1]benzopyrans (7a-c) in the presence of ammonium acetate and acetic acid proceeded smoothly and gave the expected 1-aryl-1*H* [1] benzopyrano[3,4-*b*] [1]benzopyrano [3',4'-*d*] pyrrole-7*(H)*-ones (9a-i) in 51-56 % yield. The structures of all the compounds (9a-i) were confirmed by analytical and spectral data.

All the compounds in their IR spectra showed a charactristic coumarin carbonyl stretching band between 1710-1725 cm^{-1}. Compounds showed a band between 3350-3370 cm^{-1} due to N-H stretching of pyrrole moiety. Compounds also showed bands around 1610cm^{-1} and 3045cm^{-1} for aromatic C=C and aromatic C-H stretchings respectively. All the compounds gave satisfactory NMR spectra (60MHz). Here it is important to mention that in the NMR spectrum of all the compounds, the signal for C_1-H was merged with the aromatic protons signals. The signal for N-H proton was also merged with the aromatic protons signal. This was confirmed by scanning the spectra after D_2O exchanged and observing the integration for the signal in the aromatic region which decreased in value for one proton.

Compound 9a

IR: λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin),3355cm^{-1}(N-Hstretching), 1615cm^{-1} (aromatic C=C stretching), 3050cm^{-1} (aromatic C-H stretching).NMR, 6.2-8.9δ(15H,multiplet,13aromatic protons + C_1-H + -NH proton merged).

Compound 9b

IR: λ_{max}1710cm^{-1}(δ-lactonecarb onyl stretching of coumarin),3350cm^{-1}(N-Hstretching),1600m^{-1} (aromaticC=Cstretching), 2940cm^{-1}(aliphatic C-H stretching of methyl group), 3035cm^{-1}(aromatic C-H stretching).NMR, 2.4δ (3*H*, singlet, -CH_3), 6.1-8.9δ (14*H*, multiplet, 12 aromatic protons+ C_1-H + -NH proton merged).

Compound 9c

IR: λ_{max}1705cm^{-1}(δ-lactone carbonyl stretching of coumarin),3365cm^{-1} (N-H stretching), 1615cm^{-1}(aromatic C=C stretching), 3060cm^{-1} (aromatic C-H stretching).NMR, 3.8δ (3*H*, singlet, -OCH_3), 6.1-8.8δ (14*H*, multiplet, 12 aromatic protons + C_1-H + -NH proton merged).

Compound 9d

IR:λ_{max}1720cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3360cm^{-1}(N-H stretching), 1610cm^{-1} (aromatic C=C stretching), 2940cm^{-1} (aliphatic C-H stretching of methyl group), 3045cm^{-1}(aromatic C-H stretching).NMR, 2.4δ (3*H*, singlet,–CH_3), 6.2-8.8δ (14*H*, multiplet, 12 aromatic protons + C_1-H + -NH proton merged).

Compound 9e

IR:λ_{max}1725cm^{-1}(δ-lactone carbonyl stretching of coumarin),3355cm^{-1}(N-H stretching), 1615cm^{-1} (aromatic C=C 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), 6.1-8.8δ (13*H*, multiplet, 11 aromatic protons + C_1-H + -NH proton merged).

Compound 9f

IR:λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin), 3365cm^{-1}(N-H stretching), 1605m^{-1} (aromatic C=C stretching), 2930cm^{-1}(aliphatic C-H stretching of methyl group), 3055cm^{-1} (aromatic C-H stretching).NMR**,** 2.3δ(3*H*, singlet, -CH_3), 3.8δ(3*H*, singlet, -OCH_3), 6.0-8.8δ (13*H*, multiplet, 11 aromatic protons + C_1-H + -NH proton merged).

Compound 9g

IR:λ_{max}1710cm^{-1}(δ-lactone carbonyl stretching of coumarin),3355cm^{-1}(N-H stretching), 1600cm^{-1} (aromatic C=C stretching), 2940cm^{-1} (aliphatic C-H stretching of methyl group), 3035cm^{-1} (aromatic C-H stretching).NMR, 2.4δ (3*H*, singlet, -CH_3), 6.1-8.8δ (14*H*, multiplet, 12 aromatic protons + C_1-H + -NH proton merged) .

Compound 9h

IR:λ_{max}1720cm^{-1}(δ-lactone carbonyl stretching of coumarin),3370cm^{-1}(N-H stretching), 1610cm^{-1} (aromatic C=C stretching), 2955cm^{-1} (aliphatic C-H stretching of methyl group), 3030cm^{-1} (aromatic C-H stretching).NMR**,** 2.4δ (6*H*, singlet, two -CH_3), 6.2-8.9δ (13*H*, multiplet, 11 aromatic protons + C_1-H + -NH proton merged).

Compound 9i

IR:λ_{max}1715cm^{-1}(δ-lactone carbonyl stretching of coumarin),3365cm^{-1}(N-H stretching), 1605cm^{-1} (aromatic C=C stretching), 2930cm^{-1} (aliphatic C-H stretching of methyl group), 3055cm^{-1} (aromatic C-H stretching).NMR, 2.3δ (3*H*, singlet, -CH_3), 3.8δ (3*H*, singlet, -OCH_3), 6.2-8.9δ (13*H*, multiplet, 11 aromatic protons + C_1-H + -NH proton merged).

Result and discusion

This series is on furanofused and pyrrolofused coumarin derivatives a brief introduction on furano and pyrrolo coumarins.After Literature survey reveals that among these types of furano coumarins, a lot of work has been carried out. While furano coumarin is not at all studied.Very first time, recently some coumarin derivatives of this class have been synthesized from our laboratory. Thus various furano[3,4-*c*]coumarins (III) have been synthesized first time. The compounds have been synthesized by demethylation cyclization of intermediates (II) which in turned were prepared by the reaction of appropriate 2-nitro-1-(2-methoxyaryl)-prop-1-enes (I) with ethyl benzoylacetate (EBA) using Nef reaction condition.Like furano coumarins the fusion of pyrrole ring to coumarin lactone ring results in a three isomeric pyrrolo coumarins i.e. pyrrolo[3,2-c]coumarin, pyrrolo[3,4-c]coumarin and pyrrolo[2,3-c]coumarin

The synthesis of 1-aryl-furano[2,3-*c*]coumarins and 1-phenyl-2-methyl-furano [2,3-*c*]coumarin (3a-e) have been carried out by reacting 3-hydroxy coumarin (1) with appropriate 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (2a-e) in the presence of piperidine using methanol as a solvent under Nef reaction condition.All compounds in their IR spectra showed a charactristic coumarin carbonyl stretching band between 1715-1725cm^{-1}. Compounds showed a band around 1120 cm^{-1}due to C-O-C stretching of furan moiety. Compounds also showed bands around 1610cm^{-1} and 3040cm^{-1} for aromatic C=C and aromatic C-H stretchings respectively. All compounds gave satisfactory NMR spectra (60MHz). The success of synthesis of various furano[2,3-*c*]coumarins prompted author to extend this methodology to synthesize pyrrolo[2,3-*c*]coumarins. Thus if 3-amino coumarin (I) is reacted with 2-aryl-1-nitro-ethenes /1-phenyl-2-nitro-propene (II) in the presence of piperidine using methanol as a solvent under Nef reaction condition then it can give 1-aryl-pyrrolo[2,3-*c*]coumarins and 1-phenyl-2-methyl-pyrrolo [2,3-*c*] coumarin

All the compounds gave satisfactory NMR spectra (60MHz). Here it is important to mention that in the NMR spectrum of all the compounds, the signal for N-H proton was merged with the aromatic protons signal. This was confirmed by scanning the spectra after D_2O exchanged and observing the integration for the signal in the aromatic region which decreased in value for one proton.

Conclusion

All synthesized compound were analysed with physico-chemical methods and confimes its structrul identity. A survey of the literature reveals that number of coumarin derivatives having heterocyclic moieties either as substituent groups or fused with parent coumarin nucleus possess 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 an active interest. The importance of these heterocoumarins and with a view to exploring new methods of synthesis.

References

1. (i) S. Shivkumar and S. Bhaduri ,*Indian journal of chemistry,* **22B**, 725, (1983). (ii)S. P. Herimath , A. S. Jivanagi and M. G. Purohit,*Indian journal of chemistry,* **32B**, 662, (1993).
2. E. Spath and F. Kuffner*Monatsch,* **69,** 75 (1936).
3. A. B. Lerner*J. Invest. Dermatol.,* **20,** 299 (1953).
4. M. A. Pathak and J. H. Fellman*Nature,* **185**, 382 (1960).
5. C. N. Patel PhD Thesis, "*synthetic studies in coumarin and coumarin based polymers",* Sardar Patel University, V.V.Nagar (2001).
6. A. K. Mitra and J. Mitra,*Indian journal of chemistry*, **33(B)**, 276-79, (1994).
7. K. N. Trivedi and R. R. Shah, *Indian journal of chemistry*, 210-12, (1981).
8. V. K. Ahluwalia, M. C. Gupta and S. Mehta, *Indian journal of chemistry*, **17(B)**, 332-335, (1979).
9. C. Majumdar, and R. De, *J.chem.Soc.Perkin Trans.1*, 1901-1905, (1989).
10. M. Maheshwari, V. K. Mahesh, R. Sharma,*Indian journal of chemistry*, **23(B)**, 486-88, (1984).
11. K. N. Trivedi and Y. A. Shikh,*J.Indian Chem.Soc.*,Vol.L, 41-44, (1973).
12. Khan, Misbahul ain, Morely, M. L. Brito,*Journal of Heterocyclic Chemistry*, **15(8)**, 1399-401, (1978).
13. V. P. PandyaPhD Thesis, "*Synthetic studies in heterocyclic substituted and fused coumarins and coumarin based polyethers",* Sardar Patel University, V.V.Nagar (2004).
14. J. M. Pepper and M. Shaha *Can. J. Chem.,* **42**, 113, (1964).
15. A. P. Bhaduri and P. K. Arora *Indian journal of chemistry*, **20(B)**, 951-54, (1981).
16. (i) F. M. Dean, A. Robertson and W. B. Whalley *J. Chem. Soc.,* 895, (1950).
(ii) K. N. Trivedi and S. Sethna *J. Org. Chem.*, **25**, 1817, (1960).
17. F. W. Linch *J. Chem. Soc.,* **101**, 1912, (1962).