# Environment Friendly One-Pot Synthesis of Pyran and Benzopyran

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## ABSTRACT

An environmentally friendly one-pot synthesis of Pyran and Benzopyran by using an activated C-H acid (4-hydroxy-coumarin), an aldehyde and malononitrile has been developed. The method uses ammonium acetate as a catalyst with water as solvent. The methods developed are simple and efficient in terms of time as well as yields.

**Keywords:** Green Chemistry, Multicomponent reaction, ammonium acetate, one-pot synthesis, 4-hydroxy coumarin

## INTRODUCTION

Green chemistry approaches to eliminate or at least reduce environmental pollution by use of synthetic methodologies which helps in keeping the environment green and clean[1] has become the need of the hour.

Amongst them, one pot multi-component synthesis has become a corner stone for developing green reactions as they bring about reduced reaction times and increased yields as compared to linear syntheses. Development of one pot synthesis for biologically active compounds has become an important area of research in organic chemistry. (Domling and Ugi, 2000; Orru and de Greef, 2003).

4-hydroxy coumarin is a class of vitamin K antagonist, anticoagulant drug molecule derived from coumarin with a hydroxyl group at the 4$^{th}$ position, formally renumbered as 2- hydroxy chromen-4-one[1,2]. When a large aromatic substituent is at the 3$^{rd}$ position it becomes an anticoagulant. It is an important fungal metabolite[1] from the precursor coumarin which itself is not an anticoagulant but it is mostly used as a perfumery agent[2].

Coumarin derivatives have revealed promising biological activity with interesting potential in therapeutic applications; besides their traditional use as anticoagulant, antifungal[1], anti-inflammatory agents[3], etc. They have also shown important properties as antibiotics (novobiocin and analogs)[4], anti-aids agents (calanolides)[5] and anti-tumor drugs[6]. Thus, coumarin derivatives form an important class of compounds, known for their diverse biological activities[7].

Pyranobenzopyrans and its derivatives are reported to possess various biological activities such as antibacterial[8], anti-fungal[9], central nervous system depressant[2], antiviral[4] and ulcer inhibitors[1], etc. SUKSDORFIN and DCK which contain Pyran and Benzopyran moiety are known to be potent anti- HIV agents[1,9].

Pyrano [2,3-d]- Pyrido [2,3-d]- pyrimidines and Pyrano [3,2-c] benzopyrans have attracted much attention owing to their biological activities[4,10]. A number of methods have been reported for their synthesis in the presence of organic bases such as piperidine or pyridine in an organic solvent (i.e., ethanol, methanol,

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pyridine). How ever most of these methods rely on multistep reactions and complex pathways, have long reaction times and have low yields[11,12,13]

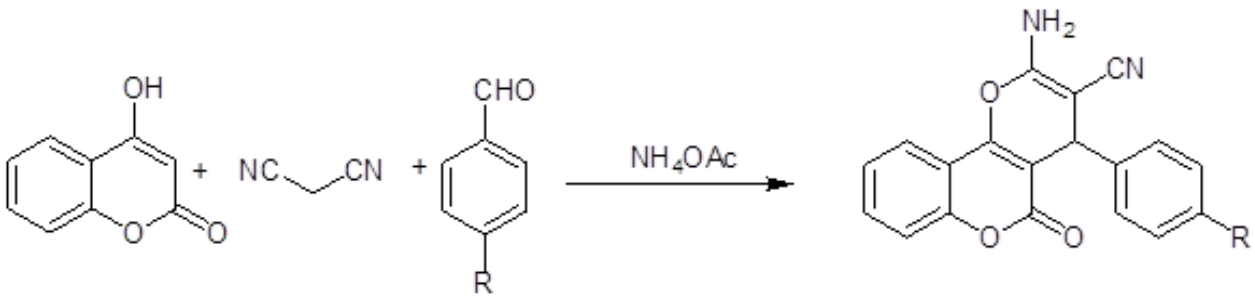
One spot synthesis of pyran-annulated heterocyclic systems from condensations of 4- hydroxycoumarin or 4-hydroxyl -6- methylpyrone or 1,3- dimethyl barbituric acid with relatively expensive reagents such as dimethyl acetylene dicarboxylate and isocyanide has also been reported in toxic benzene under reflux conditions[9,14,15].

In addition, a new method based on a multi-component reaction strategy using microwave heating in the solid state has been reported[16]. Nevertheless, the use of a green solvent such as water, which shows both economical and synthetic advantages, is desirable[17].

Further reasons that make water unique compared to other organic solvents are that it is inexpensive, non-flammable and naturally occurring; and most importantly, it is a non-toxic solvent [18].

Even though ammonium acetate is used as a catalyst in the synthesis of pyranobenzopyrans,[20], use of water as a solvent and under solvent less conditions is not reported.

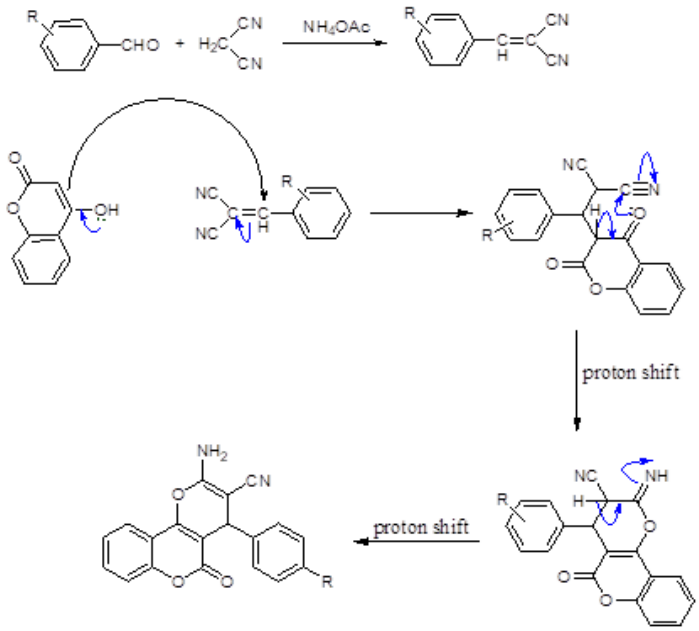
**Reaction**




1 2 3 4

Depending on the R', the time required for the reaction completion varied. The reaction goes much faster with 4- nitrobenzaldehyde and is the slowest with p-methoxy benzaldehyde.

**Mechanism:** Ammonium acetate catalyzes the condensation of the aldehyde and malononitrile resulting in the condensation product.



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# MATERIAL AND METHODS

**Representative experimental procedures with benzaldehyde have been outlined below**

**Method A: Heating At 80˚c**

4-hydroxycoumarin (0.250g,0.0015moles), malononitrile (0.101g,0.0015moles), benzaldehyde (0.163g,0.0015 moles) and ammonium acetate (0.088 g,0.0005 moles) were taken in a round bottom flask with a magnetic bob in it. The reaction mixture was heated at 80˚C using a paraffin bath on a magnetic stirrer and hot plate to obtain Pyran and Benzopyran The reaction progress was monitored using TLC. The reaction reached completion in 20 minutes. The same procedure was used with different aldehydes to obtain the corresponding Pyran and Benzopyran

| | | Method- A | | |
|---|---|---|---|---|
| R | **Product** | **Time(Min)** | **% Yield** | **M.P.(˚c)** |
| **-H** | **4a** | **20** | **83.16** | **266-268*** |
| **-Nitro** | **4b** | **15** | **80.78** | **257-259*** |
| **-Methoxy** | **4c** | **45** | **84.43** | **237-240*** |
| **-Bromo** | **4d** | **30** | **75.04** | **250-255*** |
| **-Hydroxy** | **4e** | **35** | **82.03** | **244-248** |
| **- Methoxynaphthyl** | **4f** | **180** | **62.15** | **200-210*** |

The Melting Points match with that of the melting points reported in the research paper[19].

**Method B: Grind Stone Chemistry**

4-hydroxycoumarin (0.250g,0.0015moles), Malononitrile (0.101g,0.0015moles), benzaldehyde (0.163g,0.0015 moles) and ammonium acetate (0.088 g) (0.0005 moles) were taken in a mortar and were ground with the help of a pestle for about 5mins and the reaction mixture was left to stand. The reaction progress was monitored using TLC. The same procedure was used with different aldehydes to obtain the corresponding Pyran and Benzopyran.

| | | Method- B | | |
|---|---|---|---|---|
| R | **Product** | Time (Min) | % Yield | M.P.(˚c) |
| **-H** | **4a** | 30 | 84.19 | 266-268 |
| **-Nitro** | **4b** | 15 | 85.45 | 257-259* |
| **-Methoxy** | **4c** | 90 | 84.43 | 237-240* |
| **-Bromo** | **4d** | 35 | 75.53 | 250-255* |
| **-Hydroxy** | **4e** | 45 | 83.98 | 244-248 |
| **-Methoxynaphthyl** | **4f** | 480 | 62.15 | 200-210* |

The Melting Points match with that of the melting points reported in the research paper[19].

**Method C: Stirring At Room Temperature**

4-hydroxycoumarin (0.250g,0.0015moles), malononitrile (0.101g,0.0015moles), benzaldehyde (0.163g,0.0015 moles) and ammonium acetate (0.088 g,0.0005 moles) were taken in a round bottom flask with a magnetic bob in it. The reaction mixture was stirred at room temperature using a paraffin bath on a magnetic stirrer plate to obtain Pyran and Benzopyran. The reaction progress was monitored using TLC. The reaction reached completion in 35 minutes. The same procedure was used with different aldehydes to obtain the corresponding Pyran and Benzopyran.

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| | | METHOD- C | | |
|---|---|---|---|---|
| R | **Product** | **Time(Min)** | **% Yield** | **M.P.(˚c)** |
| **-H** | **4a** | **35** | **83.78** | **266-268** |
| **-Nitro** | **4b** | **20** | **86.17** | **257-260*** |
| **-Methoxy** | **4c** | **150** | **84.61** | **237-240*** |
| **-Bromo** | **4d** | **60** | **75.04** | **250-255*** |
| **-Hydroxy** | **4e** | **120** | **82.42** | **244-248** |
| **-Methoxynaphthyl** | **4f** | **360** | **61.60** | **200-207** |

The Melting Points match with that of the melting points reported in the research paper[19].

**Method D: Heating At 80 ˚c With Water**

Malononitrile (0.101g,0.0015moles), benzaldehyde (0.163g,0.0015 moles) and ammonium acetate (0.088 g,0.0005 moles) and 20 cm $^3$ of water was taken in a round bottom flask and heated at 80 ˚C using a paraffin bath and magnetic stirrer- hot plate. After 10 minutes 4- hydroxycoumarin (0.250g,0.0015 moles) was added to the reaction mixture and heated at 80 ˚C for 20 minutes to obtain Pyran and Benzopyran. The reaction progress was monitored using TLC. The reaction reached completion in 20 minutes.

The same procedure was used with different aldehydes to obtain the corresponding Pyran and Benzopyran.

| | | METHOD- D | | |
|---|---|---|---|---|
| **R** | **Product** | **Time (Min)** | **% Yield** | **M.P. (˚c)** |
| **-H** | **4a** | **40** | **84.19** | **266-269*** |
| **-Nitro** | **4b** | **30** | **80.78** | **257-262*** |
| **-Methoxy** | **4c** | **135** | **84.61** | **237-242*** |
| **-Bromo** | **4d** | **60** | **77.33** | **250-254** |
| **P- -Hydroxy** | **4e** | **150** | **82.03** | **244-247** |
| **-Methoxynaphthyl** | **4f** | **300** | **60.00** | **200-205** |

The Melting Points match with that of the melting points reported in the research paper[19].

To study the effect of the catalyst in the synthesis of above mentioned Pyran and Benzopyran we have carried out their synthesis in water as reported[19] and compared the results obtained with the results of the protocol developed by us. The procedure and the results are given below.

**Comparative study of Method D and E**

**Method E: Typical Procedure For The Preparation Of 4a As Reported.**

The mixture of malononitrile(0.066g,1mmol) and benzaldehyde(0.106g,1mmol) in 20mL of distilled water was stirred for 3hours at 80˚**C.**The reaction mixture was cooled and 4-hydroxy coumarin(0.162g,1mmol) was added in small portions. Stirring was continued for 9.5Hrs. The progress of the reaction was monitored using TLC.

The same procedure was used with different aldehydes to obtain the corresponding Pyran and Benzopyran.

| **R** | **P** | **Method-E** | | | **Method- D** | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Time (Hrs)** | **Yield (%)** | **M.P. (˚c)** | **Time (Min)** | **Yield (%)** | **M.P. (˚c)** | |
| **-H** | **4a** | **13** | **77** | **266-268** | **30** | **84.9** | **266-267** | **4a** |
| **-Nitro** | **4b** | **10** | **70** | **256-268** | **20** | **85.45** | **257-260** | **4b** |
| **-Methoxy** | **4c** | **14** | **69** | **234-238** | **90** | **85.36** | **237-240** | **4c** |

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## RESULTS AND DISCUSSION

We have developed four environmentally friendly, simple and efficient protocols for one- pot synthesis of pyranobenzopyrans by using an activated C-H acid (4-hydroxy-coumarin), an aldehyde and malononitrile with ammonium acetate as a catalyst under solventless conditions and also using water as a solvent.

All the methods gave products in good yields while the time required and thereby the energy consumption is considerably less. The addition of ammonium acetate as a catalyst has greatly enhanced the rate of the reaction.

Depending on the substituent on the aldehyde, the time required for the reaction completion varied. The reaction goes much faster with 4- nitrobenzaldehyde and is the slowest with p-methoxy benzaldehyde.

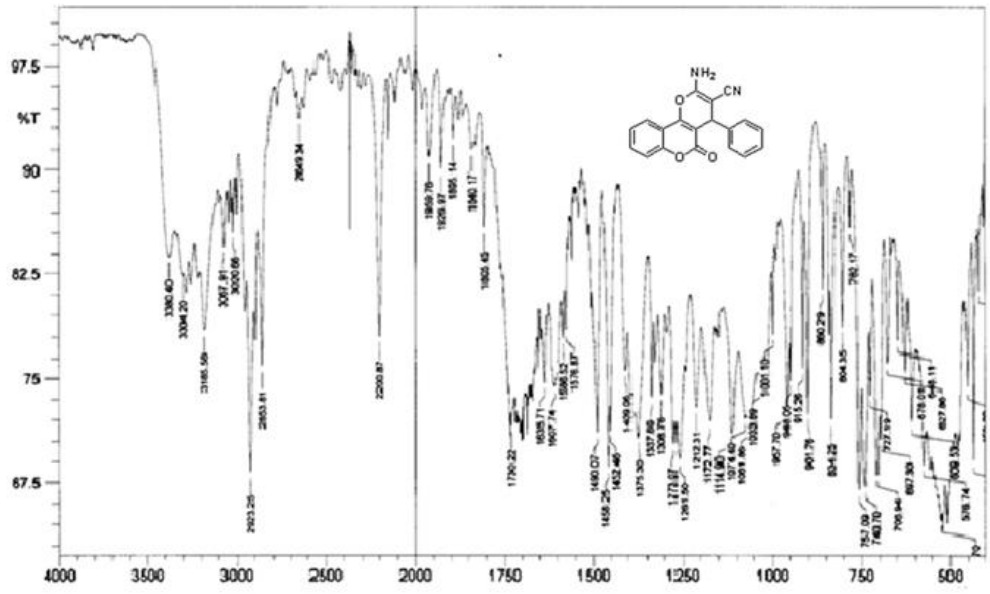
Use of a catalyst showed the greatly improved yields and time taken for the reaction.

Following are the simple and efficient protocols for the synthesis of Pyran benzo pyrans that were developed:

1. Stirring at room temperature
2. Grind Stone Chemistry
3. Heating at 80ºC
4. Stirring at 80˚C with water as a solvent

The synthesized Pyran and Benzopyran was characterized by IR spectroscopy.

**Interpretation: IR spectrum of 2-amino-3-cyano-4-(phenyl)-4H, 5H-Pyrano-(3,2-c)benzopyran-5-one(4a)**




**Interpretation Of Ir Spectrum Of Compound 4a**

The twin peak at 3500-3100cm$^{-1}$is due to of -$NH_2$group.

The sharp peak at 2200.87 cm$^{-1}$is due to –CN group.

The peak at 3000 cm$^{-1}$is due to aromatic –C-H stretch.

The peak at1730.22cm$^{-1}$is due the –CO group of the lactone ring.

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## CONCLUSION

In summary we have developed a sequential one pot synthesis of pyranobenzopyrans using green chemistry. The protocols are simple and efficient, giving good yields. The ease of work up together with the use of inexpensive and efficient base catalyst is the notable feature of the protocol. Thus, the protocol shows both economical and synthetic advantages and is eco-friendly.

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