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Research Article

Mechanism and Kinetics of Novel Coumarin Derivatives Production for Pharmaceutical Applications

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Abstract: Naturally coumarins have some bioactivity and commonly used among traditional medicine recipes against diabetes and hepatitis diseases. In addition to their derivatives that possess high importance due to their biological activity, therefore they are induced in the pharmaceutical industry as anticoagulant, antimicrobial, anti-inflammatory, antiviral, antioxidant and analgesic compounds. In this study, the formation of coumarin derivatives, which involved in pharmaceutical industries, was passed through by studying their method of preparation, mechanism of their preparative reactions and the study of their rate of reactions. Reactions were demonstrated subsequently by obtaining the product to be obtained for the next one and starting from coumarin synthesis.

Keywords: Coumarin derivatives, kinetics, mechanism, pharmaceutical applications

INTRODUCTION

The term novel coumarin comes from "novel" a Latin origin word "Nuvos" which means "new", while Coumarin is a natural organic chemical compound from benzopyrone family, coumarin derivatives are the new compounds derived from the reaction of coumarin natural or synthetic compound with another interoperated chemical compounds (Murray *et al*., 1982).

The coumarin derivatives possess high importance due to their biological activity, therefore they are induced in the pharmaceutical industry as anticoagulant, antimicrobial, anti-inflammatory, antiviral, antioxidant and analgesic compounds (Edardes, 2008).

Coumarin name comes from word "coumarou" the common name of Tonka beans, from which coumarine is extracted, the coumarins derivatives are lactones containing compounds with attachment of benzopyrone ring, the coumarins could be either lab-synthesized or extracted from origin plants, the Coumarin-containing supramolecular medicinal agents as a new increasing expansion of supramolecular chemistry in pharmaceutical science have also been actively investigated in recent years. Coumarin-derived artificial ion receptors, fluorescent probes and biological stains are growing quickly and have a variety of potential applications in monitoring timely enzyme activity, complex biological events as well as accurate pharmacological and pharmacokinetic properties. As anticoagulant, antineurodegenerative, anticancer, antioxidative, antibacterial, antifungal, antiviral, antiparasitic, antiinflammatory and analgesic, antidiabetic, antidepressive and other bioactive agents as well as supramolecular medicinal drugs, diagnostic agents and pathologic probes and biological stains. Some rational design strategies, structure-activity relationships and action mechanisms are discussed. The perspectives of the future development of coumarin-based.

Current Developments of Coumarin Compounds in Medicinal Chemistry-Research Gate. Available from: http://www.researchgate.net/publication/235728655_Current_Developments_of_Coumarin_Compounds_in_Medicinal_Chemistry [accessed Oct 8, 2015] derivation of coumarin substituted compounds enhance the coumarins bioactivity making (Shah *et al*., 2011).

Naturally coumarins also have some bioactivity and commonly used among traditional medicine recipes against diabetes and hepatitis diseases, they occur in seeds and leaves of many species of plants as result of secondary metabolism reaction (El-kasem, 2002).

Scope on novel coumarin derivatives: Coumaromycin, Novobiocin and Chartesium are coumarins derivatives of importance that have aroused nowadays for using them in biochemical determination of enzymes due to their fluorescent nature (Atta-Ur-Rahman *et al*., 2009).

They are various methodologies for obtaining coumarin derivatives; one of the most common methods is Knoevnagel condensation alongside with Claisen rearrangement, Perkin reaction, Pechmann reaction and Witting reaction (El-kady, 2002).

Experiments demonstrated that microwave irradiation help promoting the reaction of coumarin derivatives synthesis and greatly favored more than

using common conventional methods of synthesis (Murray *et al*., 1982).

Coumarin heteroaryl and benzoic compounds possess different bioactivity degrees, which could be complied in many broadband of pharmaceuticals and dyes industries.

Chalcones of coumarins in solvent media also possesses antibacterial activity (Shah *et al*., 2011). Coumarins when under goes the side chain reaction with fluoro compounds enhance the biological activity of coumarins, thus because the corporation of florin with heterocyclic compounds in general increase its bioactivity (El-kasem, 2002).

Sulfonamide moieties when introduced to coumarins shows a very strong antibacterial activity, sulfonamide moieties on its solo is a well-known antibacterial active compounds, Specially 1, 5 benzoic thiazepine shows numerous biological activity like antitumor, antimicrobial, antihypertensive, calcium channel blocker, blood platelet aggregation inhibitors (Edardes, 2008).

To count coumarins derivative is too many and with wide variety and versatile broadband applications ranging from dyes manufacturing, to bio-pharmacy commercial compounds, from simple anti-inflammatory to even the most advanced diabetes medicines (Atta-Ur-Rahman *et al*., 2009).

Through this study, the synthesis of new coumarin derivatives will be discussed besides its kinetics and mechanism of reaction, for compounds which used in pharmaceutical industry as mainly as antibacterial and anti-inflammatory compounds (El-kasem, 2002). It is important to notice that coumarins are very abundant compounds in the nature found in many plants seeds and roots, which means on derivation of this compounds and inducing the in the pharmaceuticals industry reduces the biological side effects of such medicines, as human bodies have previous experience dealing with coumarins and its derivatives (Veshik, 2011).

Coumarins derivatives found to be safe and effective compounds to all ages with almost no significant side effects.

It should be noted that all the following reactions procedures are carried on lab scale, where the procedures are completely different upon transferring to plant scale production (Atta-Ur-Rahman *et al*., 2009).

MATERIALS AND METHODS

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarins is beyond the scope of this study.

Experimental Data obtained in this using MATLAB® software based on results obtained by many studies.

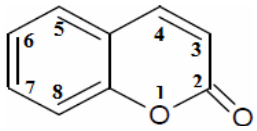


Fig. 1: Coumarine structural formula

Mechanism and kinetics study of novel coumarin reactions: Pure native Coumarin is a heterocyclic compounds with molecular formula $C_9H_6O_2$ its related to benzopyrone chemical class the structure formula of coumarin with carbon atom conventional numbering is showed in the following Fig. 1.

In this study, the formation of coumarin derivatives, which involved in pharmaceutical industries, will be passed through, thus by studying their method of preparation, mechanism of their preparative reactions and the study of their rate of reactions (Murray *et al*., 1982).

Reactions are going to be demonstrated subsequently, i.e., using the previously obtained product to obtain the next one and starting from coumarin synthesis.

There are mainly thirteen novel coumarin derivatives compounds, where six of them are mainly used in pharmaceuticals as anti-inflammatory and anti-bacterial products (Murray *et al*., 1982):

- 7-Hydroxy-4-Methyl Coumarin
- 8-nitro-7-Hydroxy-4-Methyl Coumarin
- 8-Amino-7-hydroxy-4-methyl Coumarin
- 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione
- 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione
- 6-methyl-2-substituted-8 H-pyrano [2, 3-e] benzoxazol-8-one

Preparation of 7-Hydroxy-4-Methyl Coumarin (Coumarin Synthesis) (Fig. 2).
Procedure (Sharma, 2011):

- 0.15 Liter of concentrated H_2SO_4 Cooled by ice external beaker till reaches 5 °C.
- 37 gm of resorcinol powder mixed with 45 mL of Ethyl acetoacetate to form smooth solution.
- The obtained solution added very slowly to H_2SO_4 so that the temperature of the mixture does not exceed 10°C with continues stirring for 35 min.
- The mixture is then poured into cold-water beaker and left for about 5 min.
- Then filtered to obtain solid product of 7-Hydroxy-4-Methyl Coumarin of yield 85%.

Product Properties (Sharma, 2011):

- Melting point: 192 5°C.
- Molecular Formula: $C_{10}H_8O_3$

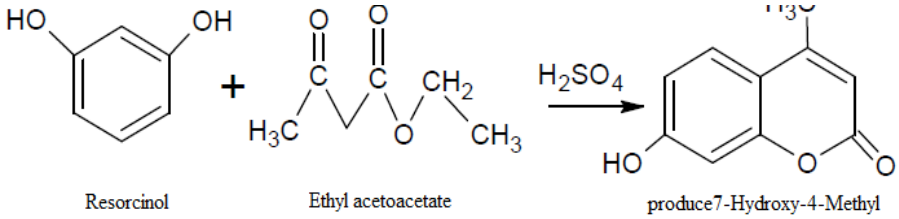


Fig. 2: Preparation of 7-Hydroxy-4-Methyl Coumarin

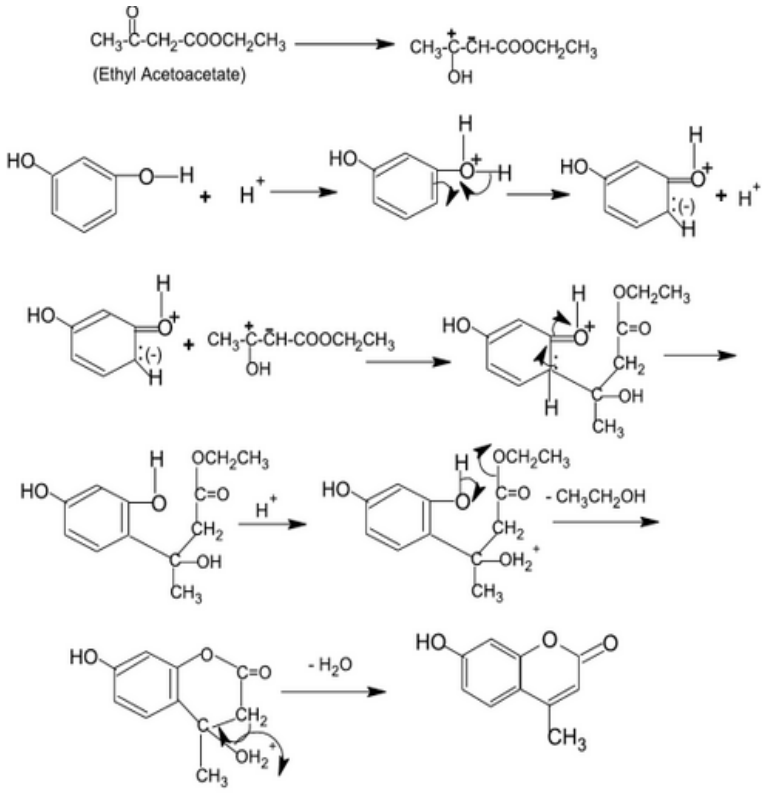


Fig. 3: Mechanism of the Hydroxy-4-Methyl coumarin synthesis by Pechmann condensation reaction

- Molecular Mass: 176.17
- Soluble in: Methanol, Ethanol, Pyridine, H_2SO_4

Mechanism of hydroxy-4-Methyl Coumarin (Ajani and Nwinyi, 2010): The Hydroxy-4-Methyl Coumarin easily obtained with the Pechmann condensation reaction discovered by the German scientist Hans Von Pechmann, the proposed mechanism will be as follow (Patil and Patil, 2011):

Figure 3, the hydroxyl group located on the 2nd carbon atom in the benzene ring gains a positive hydrogen ion from H_2SO_4, this leads to obtain un stable compound, this intermediate compound tends to stability by transferring the gained hydrogen atom from 2nd to 3rd carbon atoms, which in turns leads to detachment of the double bond in this position with a negative charge formed on this intermediate compound (Patil and Patil, 2011).

In ethyl acetoactate a hydrogen atom is internally transferred to the double bound between the oxygen and carbon atom in the ethyl group with a positive charge atom (Ajani and Nwinyi, 2010).

The two intermediate compounds formed is then attracted together to form more stable compound, then the double bond formed in the hydroxyl group exist on the benzene ring is re-opened to be able to form the new ring of benzene leading to formation of coumarin with releasing a water molecule (Atta-Ur-Rahman *et al*., 2009).

Kinetics model f 7-hydroxy-4-methyl Coumarin (Kavimani *et al*., 2000): Main reaction is:

$$C_6H_6O_2+24\ C_6H_7O \rightarrow 15\ C_{10}H_8O_3+27\ H_2O$$

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarins is beyond the scope of this study.

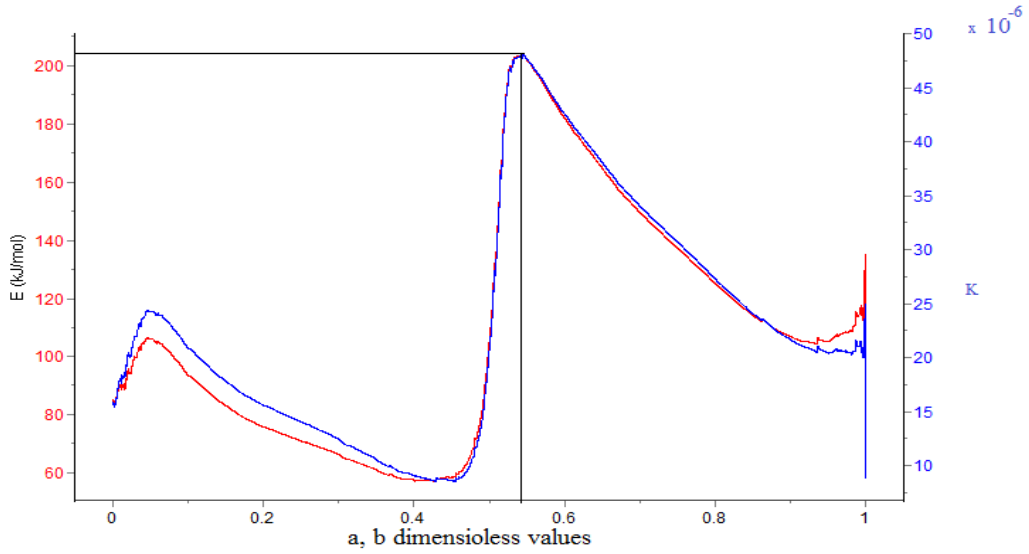


Fig. 4: Activation Energy (E) and rate constant experimental values for 7-Hydroxy-4-Methyl Coumarin formation

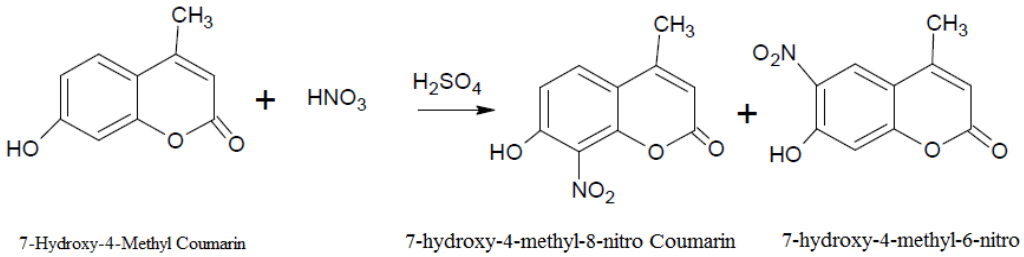


Fig. 5: Nitration reaction of 7-hydroxy-4-methyl coumarin

Experimental data obtained in this graph using MATLAB® software based on results obtained by (Kavimani *et al*., 2000):

$$\text{Rate(r)} = \frac{-d\ C6H6O}{dt} = k\ [C_6H_6O_2]^a\ x\ [C_6H_7O]^b$$

$$K = Ae^{-Ea/RT}$$

$$\ln K = \ln A - Ea/RT$$

According to experiments the following graph obtained, Fig. 4.

For the maximum yield of the reaction, the optimum value of activation energy is at the peak of the graph obtained E = 205 KJ/mol correspond to a = b = 0.55 and $k = 48\times10^{-6}$.

By substation in the above equation where value of Arrhenius pre exponent factor (A) could be neglected and the value can be got through T = 283 K = 10°C.

Due to exothermicity of sulfuric and water side reaction while preparation, the temperature should not exceed 10°C to obtain the maximum yield.

Preparation of 8-nitro-7-hydroxy-4-methyl coumarin: Upon the nitration of 7-Hydroxy-4-Methyl Coumarin with concentrated nitric acid in presence of concentrated sulfuric acid, yields the production of two nitro isomers of 7-Hydroxy-4-Methyl Coumarin, which is 7-hydroxy-4-methyl-6-nitro Coumarin and 7-hydroxy-4-methyl-8-nitro (Fig. 5) where the late compound is more desirable in pharmaceutical industry (El-kady, 2002).

Procedure (Nachiket *et al*., 2010):

- Twelve gram of 7-Hydroxy-4-Methyl Coumarin is added to 0.1 L of H_2SO_4 in beaker surrounded by ice so that the temperature during process not exceeding a temperature of 1°C.
- Nitrating agent is prepared by adding 5 mL of concentrated nitric acid very slowly to a 15 mL of concentrated in a ice cooled beaker.
- The two mixture obtained from the two previous steps are mixed slowly taking in consideration that the temperature not exceeding 20°C inside he beaker.
- The mixture leaved to cool room temperature for 1 h with well shaking every ¼ h, then pour it into crushed ice breaker with continuous stirring.
- The solid product filtered to obtain a mixture of 7-hydroxy-4-methyl-6-nitro Coumarin and 7-hydroxy-4-methyl-8-nitro coumarin.
- The crude is washed with cold water for purification purpose and then added to ethanol boiling in conical flask.

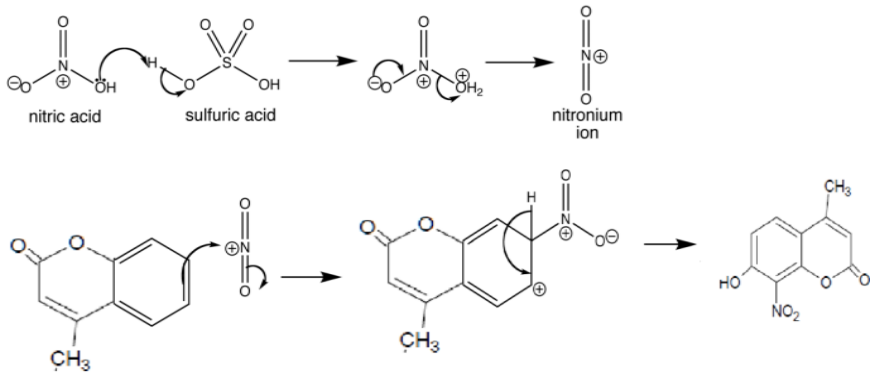


Fig. 6: Mechanism of 8-nitro-7-Hydroxy-4-Methyl Coumarin formation

- The crude and ethanol left to cool to room temperature.
- The mixture is filtered and the over product is 7-hydroxy-4-methyl-8-nitro coumarin and the residual is 7-hydroxy-4-methyl-6-nitro.
- The yield of 7-hydroxy-4-methyl-8-nitro coumarin is 60%.

Product Properties (Murray *et al*., 1982):

Melting point: 255°C
Molecular Formula: $C_{10}H_7NO_5$
Molecular Mass: 221.17

Mechanism of 8-nitro-7-hydroxy-4-methyl coumarin formation: The nitration mechanism of 7-Hydroxy-4-Methyl Coumarin follows the same patterns of benzene ring nitration, as shown in Fig. 6 the nitric and sulfuric acid groups together to form nitronium ion, where it attacks the coumarin ring at the 8th position, where the hydrogen atom is substituted by the nitro group (Khadse and Kakde, 2011).

The appearance of 6-nitro-7-Hydroxy-4-Methyl Coumarin formation can be explained by the presence of activated carbon atom when the mixture became saturated with the 8-nitro-7-Hydroxy-4-Methyl Coumarin, the carbon atom then become electron repelling and tends to attract the nitro group, this explains clearly why 8-nitro-7-Hydroxy-4-Methyl Coumarin yield is higher than 6-nitro-7-Hydroxy-4-Methyl Coumarin yield (Rajasekaran *et al*., 2011).

Kinetics of 8-nitro-7-hydroxy-4-methyl coumarin:

$$C_{10}H_8O_3+HNO_3 \rightarrow C_{10}H_7NO_5+H_2O$$

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarin derivatives is beyond the scope of this study.

Experimental Data obtained in this graph using MATLAB® software based on results obtained by (Kavimani *et al*., 2000):

$$\text{Rate(r)} = \frac{-d\ C10H7NO5}{dt} = -k\ [C_{10}H_8O_3]^a \text{ x } [HNO_3]^b$$

$k = Ae^{-Ea/RT}$
$\ln k = \text{LnA-Ea/RT}$

According to experiments the following graph obtained:

$$\text{Rate(r)} = \frac{-d\ C10H8O3}{dt} = k\ [C_{10}H_8O_3]^a \text{ x } [HNO_3]^b$$

$K = Ae^{-Ea/RT}$
$\ln K = \text{LnA-Ea/RT}$

According to experiments the following graph obtained (Fig. 7).
Taking interpolation of any 2 values of E as follow:

E = 7 KJ/mol correspond to a = 0.1 and
$k = 42\times10^{-6}$
E = 205 KJ/mol correspond to b = 0.38 and
$k = 20\times10^{-6}$

Calculate two rate of reaction (r) from:

$$r = -k\ [C_{10}H_8O_3]^a \text{ x } [HNO_3]^b$$

$$\int dt = \int_{2.33}^{8.22} \frac{-k\ [C10H8O3\ ]^a \text{ x } [HNO3]^b}{d\ CC10H8O3}$$

t = 0.98666 h approximately 1 h

Preparation of 8-amino-7-hydroxy-4-methyl coumarin: The 8-Nitro7-hydroxy-4-methyl Coumarin obtained by the reduction of the nitro group linked in the 8th position of 8-nitro-7-Hydroxy-4-Methyl Coumarin (Fig. 8).
Procedure (Ajani and Nwinyi, 2010):

- 20 mL of ethanol is added to 30 mL of concentrated hydrochloric acid
- Eight grams of iron powder is mixed portion by portion to 4.4 g of 8-Nitro7-hydroxy-4-methyl Coumarin
- The ethanol-HCl micture is poured with quick stirring to the powder mixtur
- The solution hetaed for 6 hours at temprature of 90°C

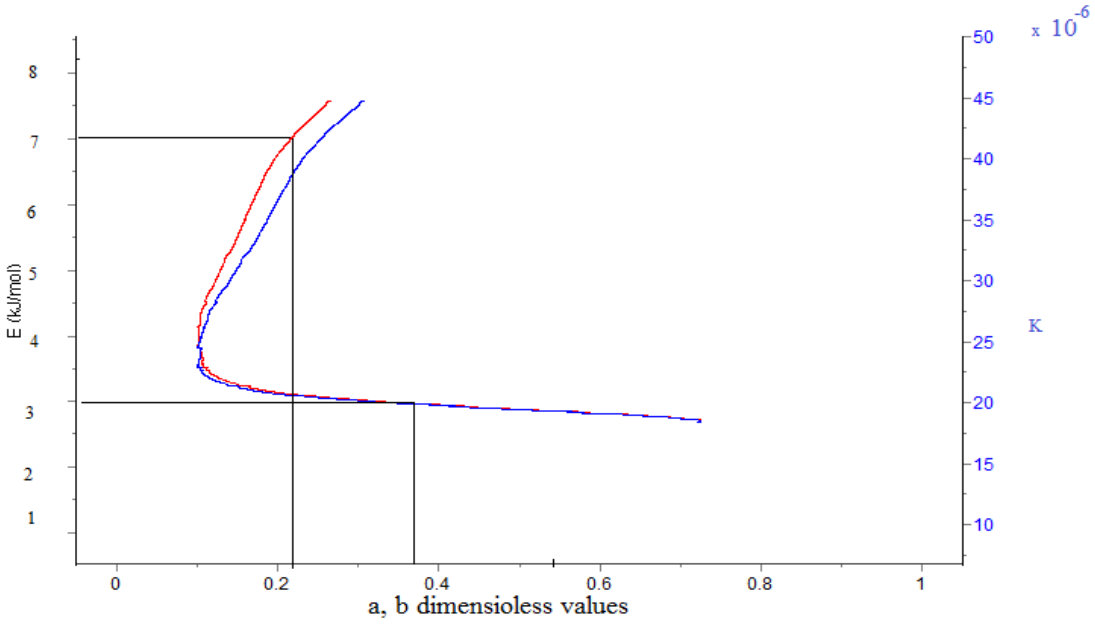


Fig. 7: Activation Energy (E) and rate constant experimental values of8-nitro-7-Hydroxy-4-Methyl Coumarin

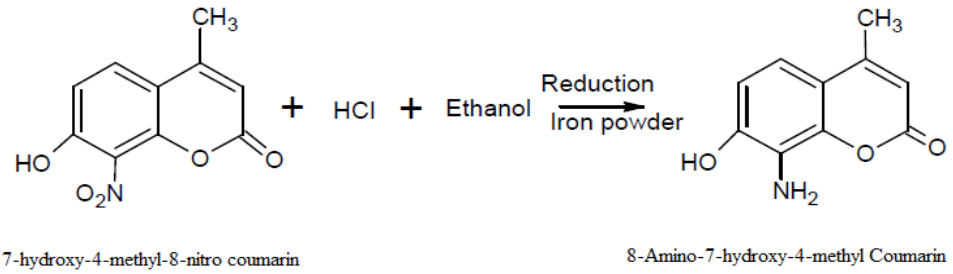


Fig. 8: Preparation of with 8-amino-7-hydroxy-4-methyl coumarin

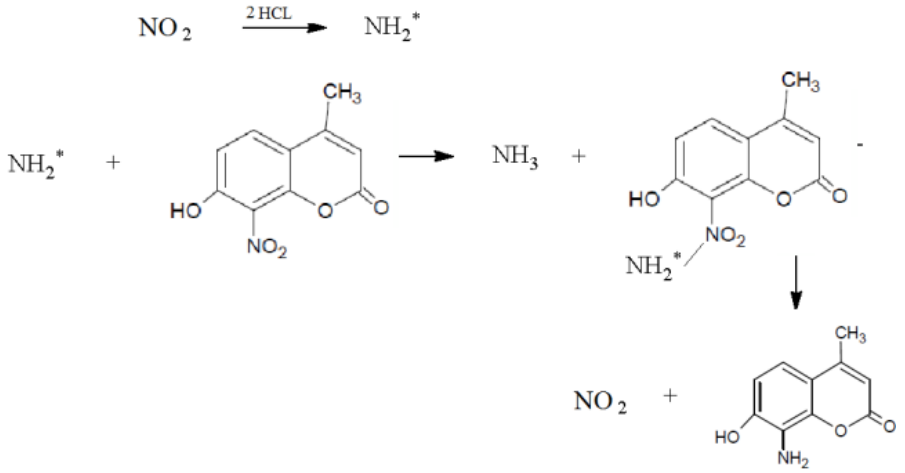


Fig. 9: Mechanism of 8-Amino-7-hydroxy-4-methyl Coumarin formation

- White precipitate is formed, filtered and washed with cold water
- The yield is 50%

Product Properties (El-kasem, 2002):

- Melting point: 280°C
- Molecular Formula: $C_{10}H_9NO_3$
- Molecular Mass: 191
- Soluble in DMF, DMSO

Mechanism of 8-amino-7-hydroxy-4-methyl coumarin: The amination of 8-nitro-7-Hydroxy-4-Methyl Coumarin formation (Fig. 9) is very simple, since the higher reactivity of NH_2 the NO2, the earlier or tends to replace the NO_2 (Sharma, 2011).

The NH_2 molecule is synthesized during the reaction, the NO_2 of 8-nitro-7-Hydroxy-4-Methyl Coumarin (Fig. 8) is isolated in the ethanol solution, then it reacts with the HCl to form NH_2 molecule which tends to attack another molecule of 8-nitro-7-Hydroxy-4-Methyl Coumarin, targeted to its NO_2 atom, this fairly explains the 50% yield of 8-amino-7-Hydroxy-4-Methyl Coumarin formation (Rajasekaran *et al*., 2011).

Kinetics of 8-Amino-7-hydroxy-4-methyl Coumarin:

$$C_{10}H_7NO_5 \rightarrow C_{10}H_9NO_3 + N_2O$$

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarins is beyond the scope of this study.

Experimental Data obtained in this graph (Fig. 10) using MATLAB® software based on results obtained by (Kavimani *et al*., 2000):

$$\text{Rate(r)} = \frac{-d\ C10H7NO5}{dt} = k\ [C_{10}H_7NO_5]^a$$

$$K = Ae^{-Ea/RT}$$

$$\ln K = \ln A - Ea/RT$$

According to experiments the following graph obtained.

Similar to nitration of coumarin, this amination reaction there is no peak activation energy, to obtain the maximum yield for this reaction; the optimum retention time will be calculated as follow.

Taking interpolation of any 2 values of E as follow:

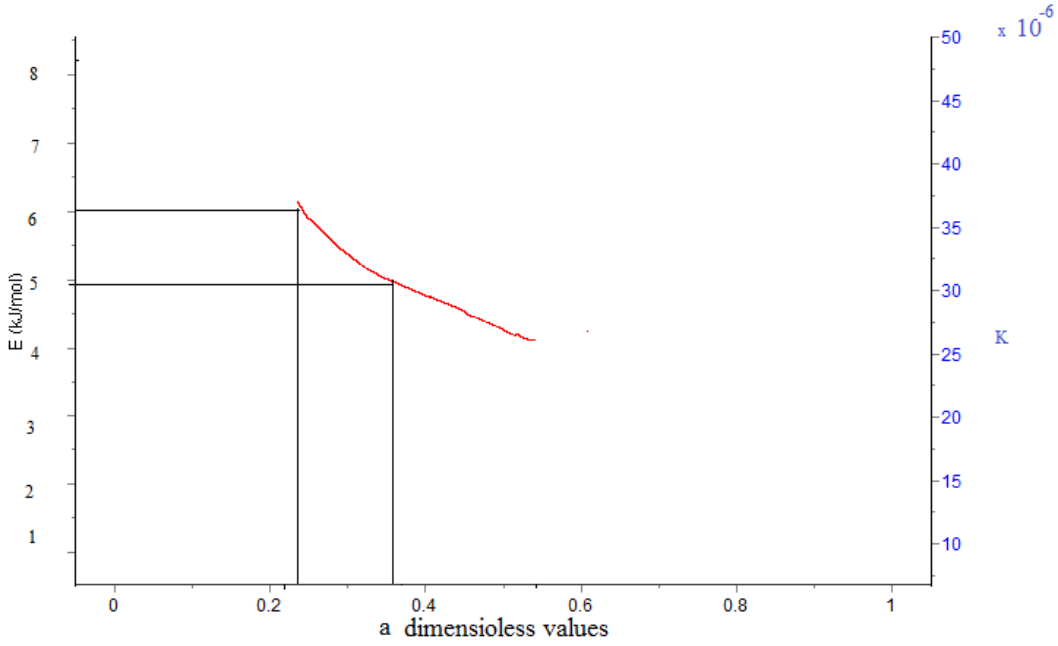


Fig. 10: Activation Energy (E) and rate constant experimental values 8-amino-7-hydroxy-4-methyl coumarin

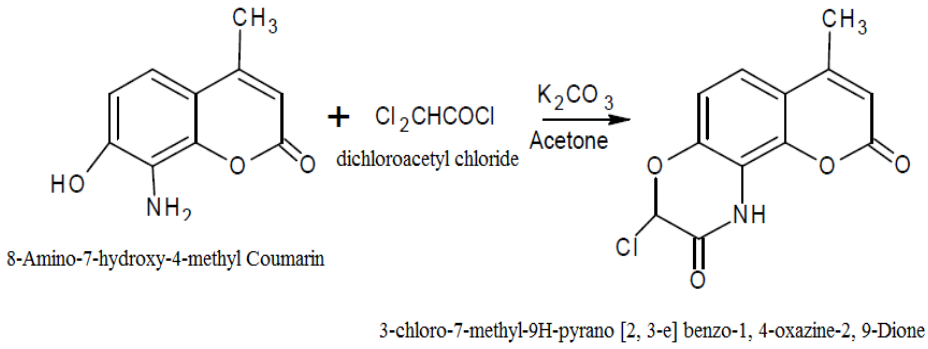


Fig. 11: Reaction of 8-amino-7-hydroxy-4-methyl coumarin with Dichloroacetyl

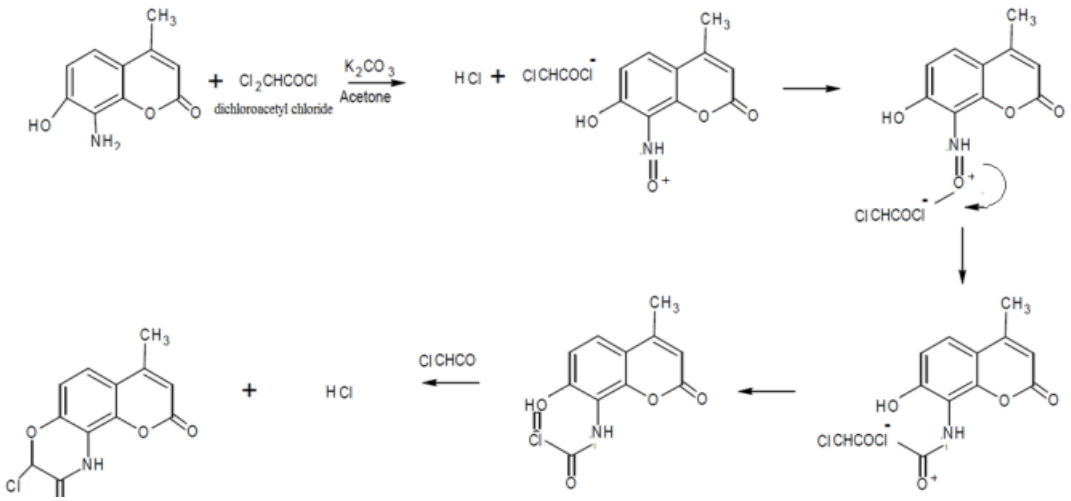


Fig. 12: Mechanism of 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione

E = 6 KJ/mol correspond to a = 2.3 and
k = 37×10^{-6}
E = 205 KJ/mol correspond to a = 2.9 and
k = 30×10^{-6}

Calculate two rate of reaction (r) from:

r = -k $[C_{10}H_7NO_5]^a$
$\int dt = \int_{2.33}^{8.22} - \llbracket$k [C10H7NO5]^a d C10H7NO5
t = 5.89 h

Preparation of 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione (Fig. 11):
Procedure (El-kasem, 2002):

- Dissolve 0.44 gm of 8-Amino-7-hydroxy-4-methyl coumarin in 0.2 mL of dichloroacetyl
- Add 0.5 gm of anhydrous potassium carbonate to 20 mL of acetone.
- Add the two previous mixtures to react together and heated at 70°C for 10 h.
- The final product is poured in cold water flask and left till completely precipitates
- A pale yellow precipitate is formed, then filtrated
- The 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione Yield is 85 %

Product Properties (More, 2011):

Melting point: 285°C
Molecular Formula $C_{12}H_8ClNO_4$
Molecular Mass: 264.1
Soluble in: Ethanol, CDCl3, DMSO

Mechanism of 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione: As shown in Fig. 12 above the amino group of 8-Amino-7-hydroxy-4-methyl coumarin is first attacked by the free radical comes from Dichloroacetyl, the oxygen radical construct a double bond with the amino group as a trend to increase the intermediate compound stability, then it tend to repel a donor electron which found by the chloro aceto group, further stability is gained through construction of double bond with the hydroxyl group to construct the benzo-oxazine group hyetero cyclic ring with release of HCl molecule out of this ring (Al-Zaydi, 2003).

Kinetics of 3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione:

$C_{10}H_9NO_3+CL_2CHCOCL\rightarrow C_{12}H_8ClNO_4+HCL$

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarins is beyond the scope of this study.

Experimental data obtained in this graph using MATLAB® software based on results obtained by (Kavimani *et al*., 2000):

Rate(r) = $\frac{-d\ C6H6O}{dt}$ = k $[C_{10}H_9NO_3]^a$ x $[CL_2CHCOCL]^b$

K = $Ae^{-Ea/RT}$
lnK = LnA-Ea/RT

According to experiments the following graph (Fig. 13) obtained. For the maximum yield of the reaction, the optimum value of activation energy is at the peak of the graph obtained E = 8.5 KJ/mol correspond to a = b = 0.65 and k = 46×10^{-6}.

By substation in the above equation where value of Arrhenius pre exponent factor (A) could be neglected and the value could be got through T = 343 K = 70°C.

Preparation of 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione (Fig. 14): Procedure (El-kasem, 2002):

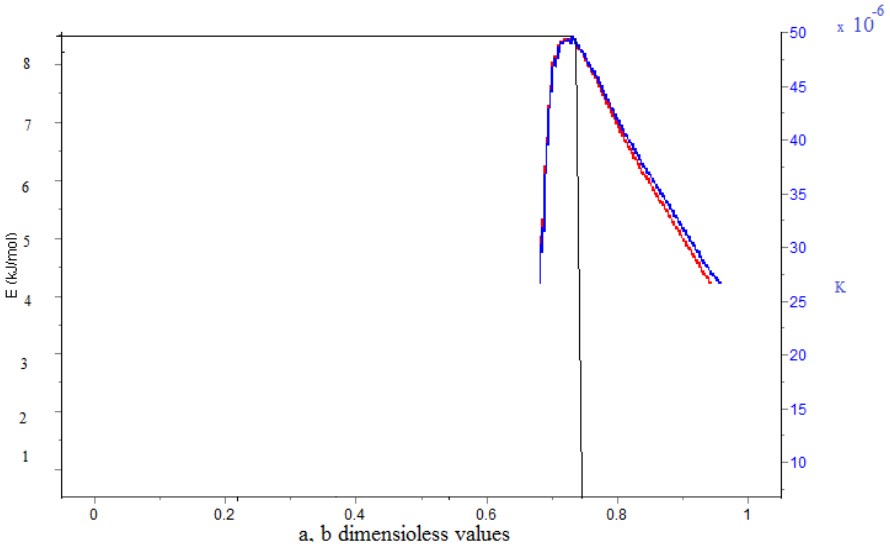


Fig. 13: Activation Energy (E) and rate constant experimental values for3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione

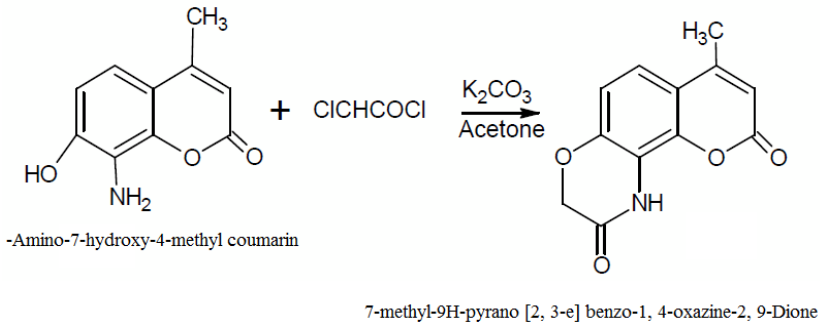


Fig. 14: Preparation of 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione

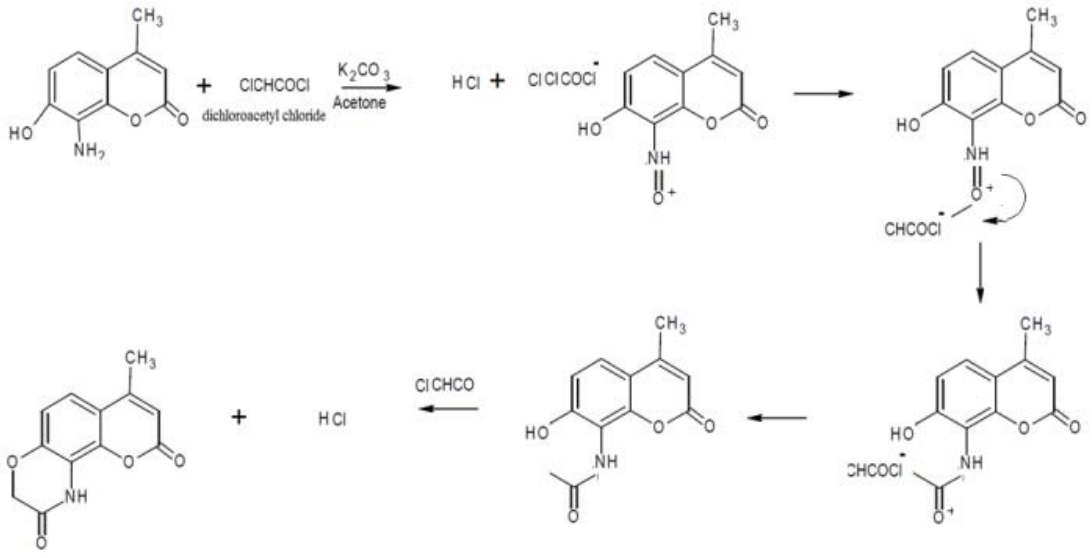


Fig. 15: Mechanism of 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione

- Dissolve 0.44 gm of 8-Amino-7-hydroxy-4-methyl coumarin in 0.17 mL of chloroacetyl chloride
- Add 0.5 gm of anhydrous potassium carbonate to 20 mL of acetone

- Add the two previous mixtures to react together and heated at 70°C for 3 h
- The final product is poured in cold water flask and left till completely precipitates
- A pale yellow precipitate is formed, then filtrated
- 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione Yield is 95%

Product Properties (El-kady, 2002):

- Melting point: 264.1°C
- Molecular Formula $C_{12}H_9NO_4$
- Molecular Mass: 230.1
- Soluble in: Ethanol, CDCl3, DMSO

Mechanism of 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione: As shown in Fig. 15 above the amino group of 8-Amino-7-hydroxy-4-methyl coumarin is first attacked by the free radical comes from chloroacetyl, the oxygen radical construct a double bond with the amino group as a trend to increase the intermediate compound stability, then it tend to repel a donor electron which found by the aceto group, further stability is gained through construction of double bond with the hydroxyl group to construct the benzo-oxazine group hyetero cyclic ring with release of HCl molecule out of this ring (Patil and Patil, 2011).

Kinetics of 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione:

$$C_{10}H_9NO_3+CLCHCOCL \rightarrow C_{12}H_9NO_4+HCL$$

For simplification of calculations, the kinetics study will be carried experimentally, as the kinetics modeling for coumarins is beyond the scope of this study.

Experimental data obtained in this graph using MATLAB® software based on results obtained by (Kavimani *et al*., 2000):

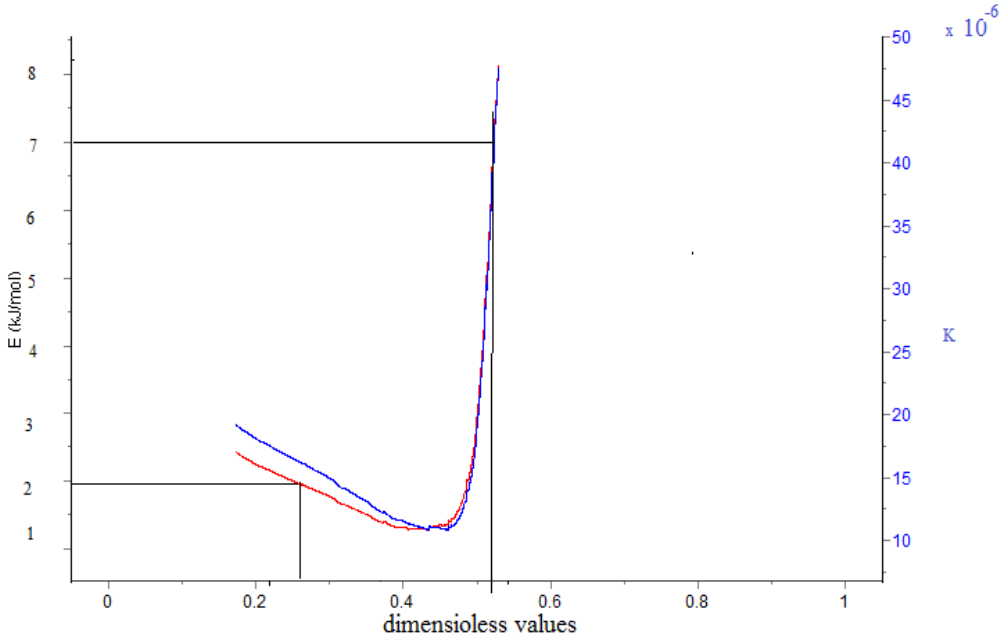
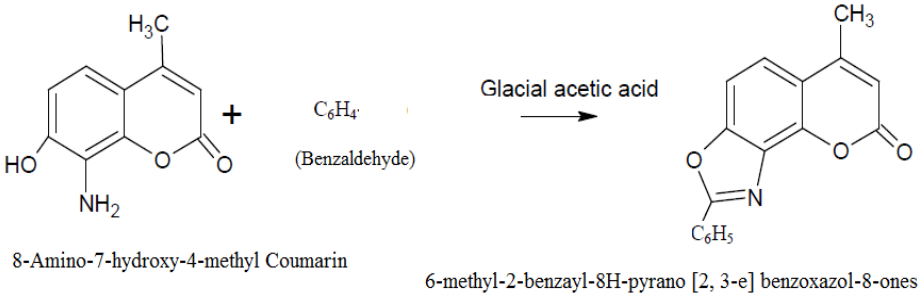


Fig. 16: Activation Energy (E) and rate constant experimental values for 7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione



8-Amino-7-hydroxy-4-methyl Coumarin

6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8-ones

Fig. 17: Preparation of 6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8H

$$\text{Rate(r)} = \frac{-d\ C6H6O}{dt} = k\ [C_{10}H_9NO_3]^a \text{ x } [CLCHCOCL]^b$$

$$K = Ae^{-Ea/RT}$$

$$\ln K = \ln A - Ea/RT$$

According to experiments the following graph (Fig. 16) obtained.

This reaction also has no peak activation energy, to obtain the maximum yield for this reaction (Fig. 16); the optimum retention time will be calculated as follow Taking interpolation of any 2 values of E as follow:

E = 7 KJ/mol correspond to a = 2.3 and
$k = 47\times10^{-6}$
E = 2 KJ/mol correspond to a = 5.2 and
$k = 15\times10^{-6}$

Calculate two rate of reaction (r) from:

$$r = \frac{-d\ C6H6O}{dt} = -k\ [C_{10}H_9NO_3]^a \text{ x } [CLCHCOCL]^b$$

(Murrey, 1982)

$$\int dt = \int_{2.33}^{8.22} -[[k\ [\ [CLCHCOCL]^{a[C10H7NO5]}$$

^b d C10H7NO5

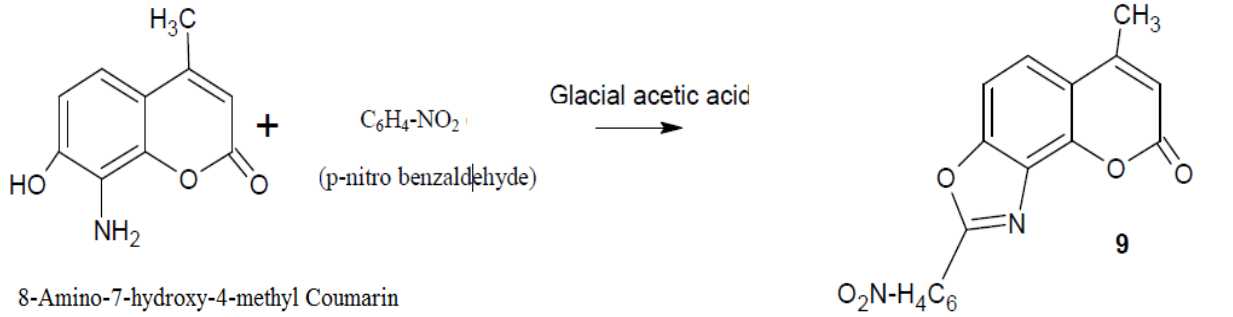
t = 2.7647 h

Preparation of 6-methyl-2-substituted-8H-pyrano [2, 3-e] benzoxazol-8-HR (Fig. 17): They are 4 products that could be obtained from the reaction of 8-Amino-7-hydroxy-4-methyl Coumarin with any of the following aldyhde:

- benzaldehyde
- p-nitrobenzaldehyde
- 4-bromo benzaldehyde
- 3, 4-dichloro benzaldehyde

Preparation of 6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8H (Fig. 17): Procedure:

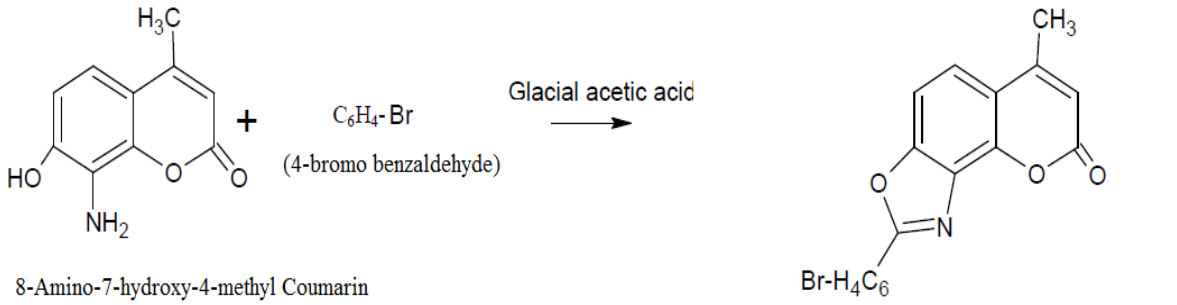
- Dissolve 5 gm of 8-Amino-7-hydroxy-4-methyl in 30 mL of in glacial acetic acid to be well shaken then stirred continuously for 5 min
- Add 3 g of benzaldehyde to the solution
- Leave the mixture for 12 h at temperature of 66-68°C
- Filter the precipitated then cool and wash with cold water
- Yield 56%



8-Amino-7-hydroxy-4-methyl Coumarin

6-methyl-2-[p-nitro benzayl]-8H-pyrano [2, 3-e] benzoxazol-8-ones

Fig. 18: Preparation of 6-methyl-2-[p-nitro benzayl]-8H-pyrano [2, 3-e] benzoxazol-8-ones



8-Amino-7-hydroxy-4-methyl Coumarin

6-methyl-2-[p-bromo benzyl]-8H-pyrano [2, 3-e] benzoxazol-8-ones

Fig. 19: Preparation of 6-methyl-2-[p-bromo benzyl]-8H-pyrano [2, 3-e] benzoxazol-8-ones

Product Properties:

- Melting point: 232°C
- Molecular Formula $C_{17}H_{11}NO_3$
- Molecular Mass: 277.24
- Soluble in: DMF and DMSO

6-methyl-2-[p-nitro benzayl]-8H-pyrano [2, 3-e] benzoxazol-8-ones: Procedure (Shah *et al*., 2011):

- Dissolve 3 gm of 8-Amino-7-hydroxy-4-methyl in 20 mL of in glacial acetic acid to be well shaken then stirred continuously for 5 min (Fig. 18).
- Add 2 g of para-nitro benzaldehyde to the solution
- Leave the mixture for 15 h at temperature of 72°C
- Filter the precipitated then cool and wash with cold water
- Yield 72%

Product Properties (El-kady, 2002):

Melting point: 245°C
Molecular Formula $C_{17}H_{10}N_2O_5$
Molecular Mass: 322.28
Soluble in: DMF and DMSO

6-methyl-2-[p-bromo benzyl]-8H-pyrano [2, 3-e] benzoxazol-8-ones: Procedure:

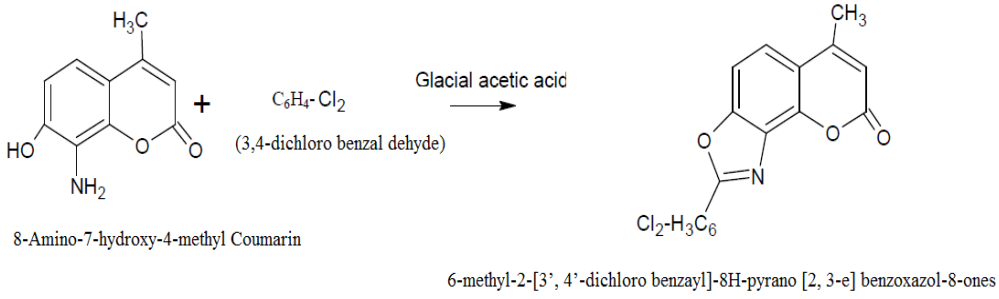
- Dissolve 5 gm of 8-Amino-7-hydroxy-4-methyl in 44 mL of in glacial acetic acid to be well shaken then stirred continuously for 5 min (Fig. 19).
- Add 7 g of 4-bromo benzaldehyde to the solution
- Leave the mixture for 9 h at temperature of 79°C
- Filter the precipitated then cool and wash with cold water
- Yield 56%

Product Properties:

Melting point: 253°C
Molecular Formula $C_{17}H_{10}BrNO_3$
Molecular Mass: 356.17
Soluble in: DMF and DMSO

6-methyl-2-[3', 4'-dichloro benzyl]-8H-pyrano [2, 3-e] benzoxazol-8-ones: Procedure (Nachiket *et al*., 2010):

- Dissolve 8 gm of 8-Amino-7-hydroxy-4-methyl in 37 mL of in glacial acetic acid to be well shaken then stirred continuously for 5 min (Fig. 20)



8-Amino-7-hydroxy-4-methyl Coumarin

6-methyl-2-[3', 4'-dichloro benzayl]-8H-pyrano [2, 3-e] benzoxazol-8-ones

Fig. 20: 6-methyl-2-[3', 4'-dichloro benzyl]-8H-pyrano [2, 3-e] benzoxazol-8-ones

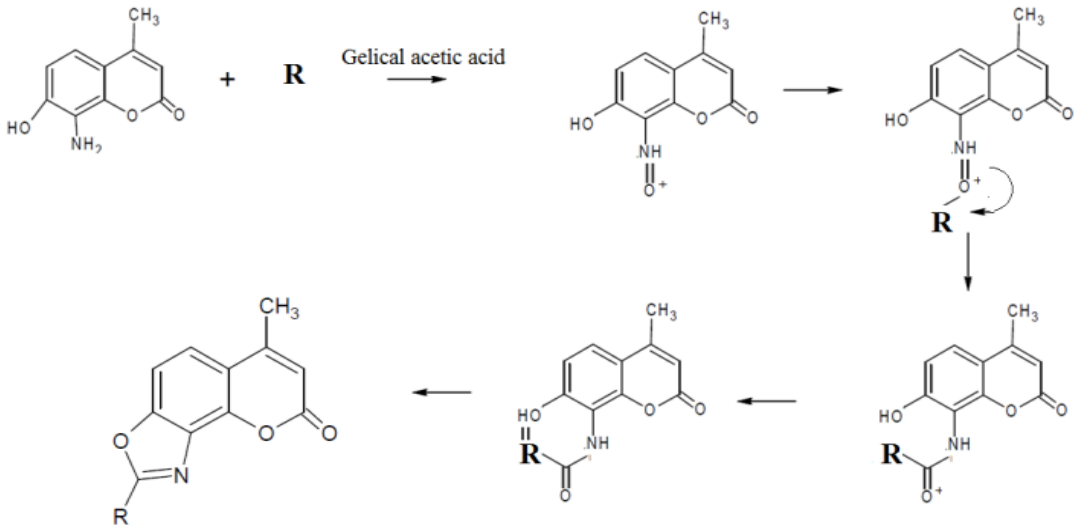


Fig. 21: Mechanism of 6-methyl-2-substituted-8H-pyrano [2, 3-e] benzoxazol-8-one

- Add 7 gram of 3,4-dichloro benzaldehyde to the solution
- Leave the mixture for 8 hours at temperature of 85°C
- Filter the precipitated then cool and wash with cold water
- Yield 56%

Product Properties (Al-Zaydi, 2003):

Melting point: 221°C
Molecular Formula $C_{17}H_9Cl_2NO_3$
Molecular Mass: 346.16
Soluble in: DMF and DMSO

Mechanism of 6-methyl-2-substituted-8H-pyrano [2, 3-e] benzoxazol-8-one: Where R could be:

- benzaldehyde
- p-nitrobenzaldehyde
- 4-bromo benzaldehyde
- 3, 4-dichlro benzaldehyde

As shown in Fig. 21 above the amino group of 8-Amino-7-hydroxy-4-methyl coumarin is first attacked by the free radical R, the radical construct a double bond with the amino group as a trend to increase the intermediate compound stability, then it tend to repel a donor electron which found by the R group, further stability is gained through construction of double bond with the hydroxyl group to construct the benzo-oxazine ring (Atta-Ur-Rahman *et al*., 2009).

RESULTS AND DISCUSSION

The rate of a chemical reaction is the time required for a given quantity of reactants to be changed to products. Usually expressed in terms of moles per unit time and affected by several factors. Nature of the reactants, concentration of the reactants, temperature, pressure and catalyst.

In this experiment the study focused on the effects of nature of the reactants. As the result were found in methods part how the structure of different coumarins effect on the mechanism and the rate of reaction.

CONCLUSION

Some coumarin derivatives, which involved in pharmaceutical industries, were studied by their method of preparation, mechanism of their preparative reactions and their rate of reactions.

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REFERENCES

Ajani, O.O. and O.C. Nwinyi, 2010. Microwave-assisted synthesis and evaluation of antimicrobial activity of 3-{3-(s-aryl and s-heteroaromatic) acryloyl}-2H-chromen-2-one derivatives. J. Heterocyclic Chem., 47: 179-187.

Al-Zaydi, K.M., 2003. Microwave assisted synthesis, part 1: Rapid solventless synthesis of 3-substituted coumarins and benzocoumarins by microwave irradiation of the corresponding enaminones. Molecules, 8(7): 541-555.

Atta-Ur-Rahman, A.B. Reitz and M.I. Choudhary, 2009. Frontiers in Medicinal Chemistry. Bentham Science Publishers, Sharjah, 4: 842-882.

Edardes, J.P., 2008. Coumarin Anticoagulant Research Progress. Nova Biomedical Books, Nova Science Poblishers, New York, pp: 1-9.

El-kady, 2002. Studies on Coumarin Derivatives. Ain Shams University, pp: 102-108.

El-kasem, A.O., 2002. Synthesis of some new coumarin derivatives of expected biological activity. Ain Shams Univ., 37: 381.

Kavimani, S., V.M. Mounissamy, R. Gunasegaran, 2000. Analgesic and anti-inflammatory activities ofHispidulir isolated from Helichrysumbracteatum. Indian drugs, 37: 582.

Khadse, C.D. and R.B. Kakde, 2011. Anti-inflammatory activity of aqueous extract fractions *of Barleria prionitis* L. roots. Asian J. Plant Sci. Res., 1(2): 63-68.

More, P.M., 2011. Indian J. Chem., 3: 747-757.

Murray, R.D.H., J. Mendez and S.A. Brown, 1982. The Natural Coumarins: Ocurrence, Chemistry and Biochemistry, John Wiley and Sons Ltd., New York, pp: 21.

Nachiket, S.D., R.P. Shashikant, S.S. Dengale, D.S. Musmade, M. Shelar, V. Tambe and M. Hole, 2010. Der Pharm. Chem., 2(2): 65-71.

Patil, V.V. and V.R. Patil, 2011. Evaluation of anti-inflammatory activity of *Ficus carica* Linn. leaves. Indian J. Nat. Prod. Resour., 2(2): 151-155.

Rajasekaran, S., G.K. Rao, S.P.N. Pai and A. Ranjan, 2011. 'Synthesis of novel coumarin derivatives and its biological evaluations'. Int. J. Chem. Tech. Res., 3(2): 555-559.

Shah, V., N. Shah and P. Shirote, 2011. Advanced Method for Synthesis of Potent Coumarin Derivatives: Design, Synthesis and Pharmacological Screening of Some Coumarin Derivatives. LAP Lambert Academic Publishing, pp: 88.

Sharma, V.A., 2011. Coumarin derivative preparation. J. Chem. Pharm., 3(2): 204-212.

Veshik, B., 2011. Issues in Pharmacology, Pharmacy, Drug Research and Drug Innovation: 2011 Edition.