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Some Aspects of the Reactivity of 3-acyl-4-hydroxycoumarins

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Abstract: Coumarins are the most important oxygenated heterocyclic of natural compounds. They are widely used as raw materials in many areas such as agrochemical, perfume, pharmaceutical industries. They therefore have several physical, chemical and biological properties. In order to enlarge this family of compounds and elucidate almost all of its properties, researchers have developed various synthetic methods that are not very complex and less expensive. Thus, from 4-hydroxycoumarin we have synthesized a series of 3-acyl-4-hydroxycoumarins by C-acylation. This study is therefore dedicated to the reactivity of 3-acyl-4-hydroxycoumarins. The synthesized coumarins showed a high reaction potential based on the chemical functions present in their structures. To enhance them later, we can try to graft other functions which can be the subject of several transformations such as: condensation, functionalization, cyclization, acylation. So to access more interesting new poly-functionalized compounds both at the reactivity and biological level. These molecules (3-acyl-4-hydroxycoumarins) being new, very little information is known on their physicochemical behavior in writings. On the other hand, the reactivity of molecules with similar structures to those of acyl-hydroxycoumarins such as 4-acylisochroman-1,3-diones and 3-acetyl-4-hydroxycoumarin have been the subject of scientists' work. It emerges from this study that 3-acyl-4-hydroxycoumarins shows strong chemical reactivity which can be used biologically.

Keywords: 4-hydroxycoumarins, C-acylation, Acyl-hydroxycoumarins, Heterocyclic Compound

1. Introduction

Coumarins are heterocyclic compounds that are abundantly present in nature. They can also be obtained by various synthetic routes. The authors have classified these compounds in several groups according to the substitutions. Hydroxycoumarins are a family of compounds very studied because of their multiple biological properties. The modification by insertion of new functions increases significantly its properties. Acylation is a method to obtain new coumarin compounds of biological interest.

C-acylation of homophthalic anhydride or isochroman-1,3-dione and O-acylation of 4-hydroxycoumarin, 3-hydroxycoumarin, 7-hydroxycoumarin and chroman-2,3-dione have already been investigated in our laboratory [1-8]. However, the products of the C-acylation of hydroxycoumarins are less studied. We therefore chose to synthesize and characterize a series of four (4) compounds of 3-acyl-4-hydroxycoumarins [9]. These compounds were synthesized by C-acylation of 4-hydroxycoumarin. In this article, we worked on the reactivity of these new synthetic compounds. We will recall the method of synthesis of these new compounds then we will discuss according to the literature the reactivity of these compounds of synthesis.

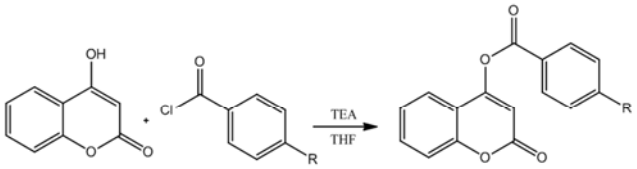
2. Synthesis of 3-acyl-4-hydroxy Coumarins

3-Acyl-4-hydroxycoumarins were synthesized from 4-hydroxycoumarin in two steps [9].

2.1. First Step: O-acylation of 4-hydroxycoumarin

2.1.1. Reaction Scheme

4-Hydroxycoumarin reacts with para-substituted benzoyl chlorides (R: para-methyl (p-CH_3), para-tertiobuthyl (p-CH_3)$_3$C), para-chloro (p-Cl) and para-nitro (p-NO_2)) in tetrahydrofuran (THF) in presence of triethylamine to form O-acyl compounds as indicated below



TEA : triethylamine; THF : tetrahydrofuran

Figure 1. *Obtaining Coumarin-4-yl Benzoate.*

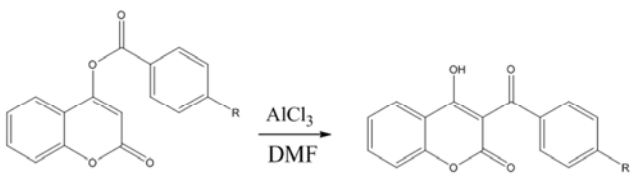
2.1.2. Operating Mode

Add to a round-bottomed flask containing 30 ml of THF, 6.17 mmol of the benzoyl chloride solution, then 3.2 ml (3.6 molar equivalents) of TEA and 6.17 mmol (1 molar equivalent) of 4-hydroxycoumarin per small portion for 30 minutes, while stirring. The reaction mixture is brought to the reflux of the solvent for 4 h. The solution obtained is poured into a separating funnel containing 40 ml of chloroform and then acidified with hydrochloric acid diluted to 10%. The organic phase is extracted and then washed with distilled water until it reaches a neutral pH; it is then dried with $MgSO_4$. After filtration, the solvent is removed in a vaccum. The product obtained is washed with hexane and recrystallized from a mixture of chloroform - hexane solvents (1/3, V / V).

2.2. Second Step: Rearrangement of the O-acylated Product into C-acylation

2.2.1. Reaction Scheme

The O-acyl compounds obtained after the first step undergo a rearrangement in DMF in the presence of a Lewis acid ($AlCl_3$) to give, after hydrolysis, the C-acyl compounds. (Figure 2).



DMF: dimethylformamide; $AlCl_3$: aluminum chloride

1: R= -CH_3; 2: R= -C-(CH_3)$_3$; 3: R= -Cl; 4: R= -NO_2

Figure 2. *Obtaining 3-benzoyl-4-hycroxycoumarin.*

2.2.2. Operating Mode

Add to a round-bottomed flask containing 30 ml of DMF, 2.24 mmol of the Coumarin-3-yl carboxylate synthesized in the first step; with gentle stirring, add 0.45g (1.5 molar equivalents) of the aluminum chloride. The reaction mixture is brought to reflux for 3 h. The solution got is poured into a separating funnel containing 40 ml of chloroform and then washed with distilled water three times. The organic phase is extracted and dried with MgSO4. After filtration, the solvent is removed. The crude product obtained is washed with hexane and recrystallized in a mixture of chloroform-hexane solvents (1/3, V / V).

3. Reactivity of Acylisochromandiones

The reactivity of 4-acylisochroman-1,3-diones has been the subject of the work of J. SCHNEKENBURGER, of R. N. USGAONKAR et al. and A. Djandé [10-13]. These researches focused on the action that certain reagents in a given medium can have on these compounds.

3.1. Action of Diazomethane in Acetone

For reasons of structural study of these compounds, by reacting them with diazomethane in acetone, J. SCHNEKENBURGER isolated the two enol ethers below [10]:

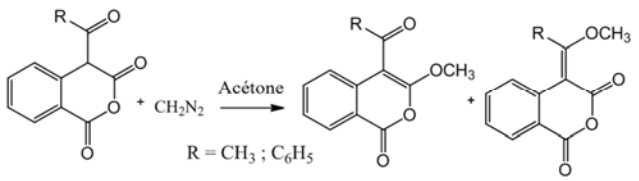


Figure 3. *Action of diazomethane in acetone (J. SCHNEKENBURGER).*

3.2. Action of Acid in Ethanol

Moreover, by treating isochromandiones in an acidic medium in ethanol, he obtained results which he described as follows [11]:

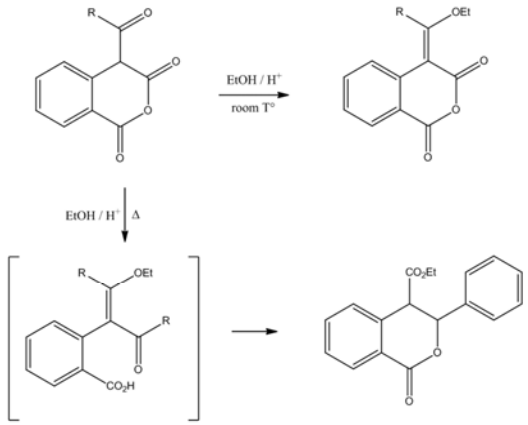


Figure 4. *Action of acid in an ethanolic medium (J. SCHNEKENBURGER).*

Thus, at room temperature, he obtains the ethyl enol ether

while at high temperature, he isolates the ethyl ester of 4-carboxy-3-phenyl-isocoumarin which would be obtained from a non-isolated intermediate of which the lactonic cycle would have opened.

3.3. Action of Acetic Anhydride

The work of R. N. USGAONKAR and Coll. made it possible to isolate an isocoumarin as the only product of the reaction, after the action of hot acetic anhydride according to the reaction scheme [12]:

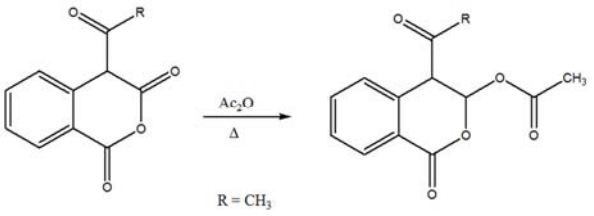


Figure 5. *Action of acetic anhydrous (R. N. USGAONKAR and Coll).*

3.4. Action of Sulfuric Acid

4-acylisochroman-1,3-diones are used for the synthesis of isocoumarins. Thus, the action of hot sulfuric acid converts these compounds, after decarboxylation, into isocoumarins with performance generally higher than 60% [12].

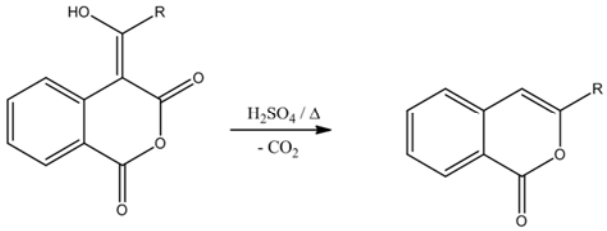


Figure 6. *Action of sulfuric acid (R. N. USGAONKAR et Coll).*

The work carried out by J. SCHNEKENBURGER and those carried out by A. SABA et Coll. indicate that in aqueous area and in the presence of sulfuric acid, 4-acylisochroman-1,3-diones are transformed into isocoumarins [13]. We notice that, at room temperature, we mainly obtain 4-carboxy-3-alkyl while at high temperature, only isocoumarin substituted in position 3 is obtained.

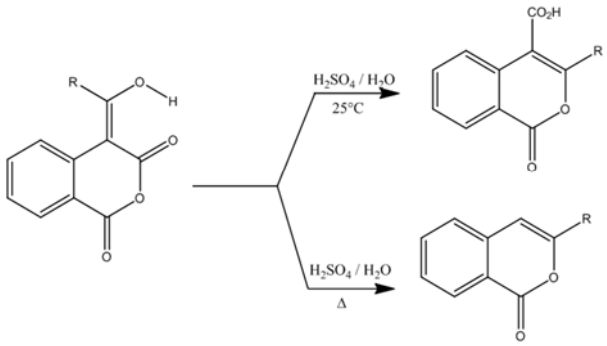


Figure 7. *Action of sulfuric acid (J. SCHNEKENBURGER).*

3.5. Action of Soda (Sodium Hydroxide) and Ammonia

These same authors (R. N. USGAONKAR and Coll) finally report the transformation of isochromandiones into 2-carboxybenzylalkyl ketones, when they are treated with sodium hydroxide in aqueous area and with isoquinolones by the action of ammonia in anhydrous area [12].

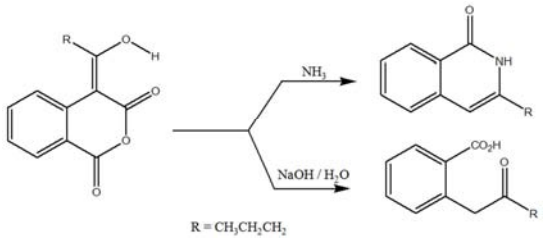


Figure 8. *Action of soda and ammonia (R. N. USGAONKAR et Coll).*

3.6. Action of Strong Base Acids on 4-acylisochroman-1,3-diones

In 2008, A. Djandé observed the action of strong acids and strong bases in non-aqueous area on 4-acylisochroman-1,3-diones [14]. Starting from the previous work, namely the action of sulfuric acid on 4-acylisochroman-1,3-diones in an ethanolic medium and at room temperature, the results obtained by A. Djandé are different from those reported by the previous authors. He obtained neither an enol ether nor a carboxy-isocoumarin, but a single compound whose identification to give the mono-ethyl ester of homophthalic acid namely 2- [2- (ethoxy- carbonyl) phenyl] acetic.

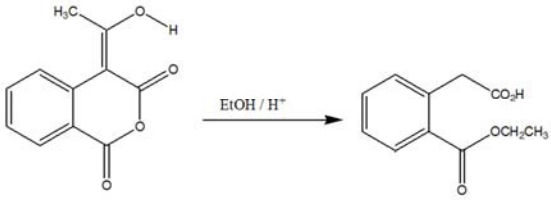


Figure 9. *Action of a strong acid (A. Djandé).*

By replacing sulfuric acid with a strong base (*sodium hydroxide*), the results are almost identical.

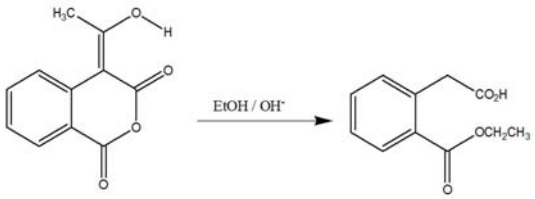


Figure 10. *Action of a strong base (A. Djandé).*

4. Reactivity of 3-acetyl-4-hydroxy Coumarin

4.1. Synthesis of 3-acetyl-4-hydroxycoumarin

3-Acetyl-4-hydroxycoumarin was synthesized by Stadlbauer and Hojas following the direct action of acetyl

chloride on 4-hydroxycoumarin in the presence of pyridine and piperidine and then taken up by J. Li et al. [15, 16].

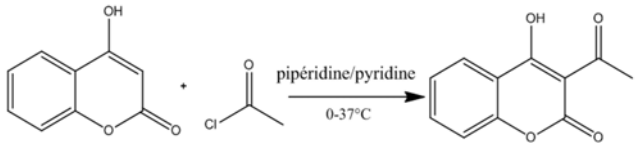


Figure 11. *Synthesis of 3-acetyl-4-hydroxycoumarin.*

4.2. Acetylation Reaction of 3-acetyl-4-hydroxycoumarin

The acetylation reaction of 3-acetyl-4-hydroxycoumarin results in a di-acetyl product (C-acyl and O-acyl) [17].

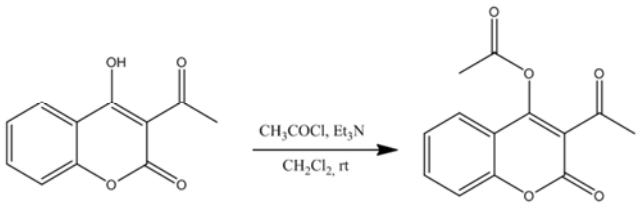


Figure 12. *Acetylation reaction.*

4.3. 3-acetyl-4-hydroxycoumarin Bromination Reaction

The bromination reaction of 3-acetyl-4-hydroxycoumarin with phenyltrimethylammonium tribromide in tetrahydrofuran gave a high performance of 3- (2-bromoacetyl) -4-hydroxycoumarin [18]. In this same study, he showed that this method of bromination is more practical compared to the means which existed in terms of safety for a large-scale application: easier control of the reaction and no release of dangerous gases.

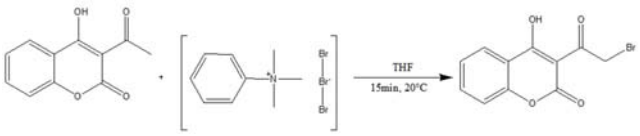


Figure 13. *Bromination reaction.*

4.4. 3-acetyl-4-hydroxycoumarin Reduction Reaction

Kappe et al. reported a simple and effective method of reducing 3-acetyl-4-hydroxycoumarin to 3-ethyl-4-hydroxycoumarin using zinc powder in a mixture of acetic acid and hydrochloric acid as a reducing agent [19].

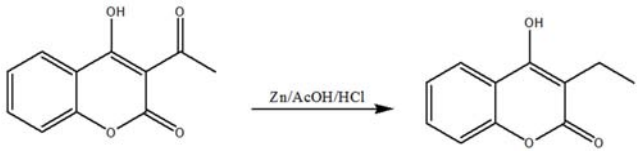


Figure 14. *Reduction reaction.*

4.5. Methylation Reaction of 3-acetyl-4-hydroxycoumarin

3-Acetyl-4-methoxycoumarin has been obtained by the methylation reaction of 3-acetyl-4-hydroxycoumarin with diazomethane at room temperature and in the presence of a catalytic amount of triethylamine [20].

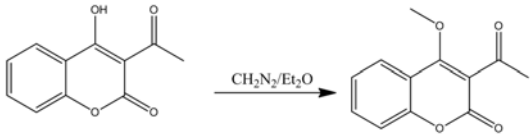


Figure 15. *Methylation reaction.*

4.6. Condensation Reaction of 3-acetyl-4-hydroxycoumarin

A series of coumarin chalcones have been synthesized by Claisen Condensation from 3-acetyl-4-hydroxycoumarin and various aryl or heteroaryl aldehydes in the presence of piperidine in chloroform, benzene, ethanol or acetic acid [21-24].

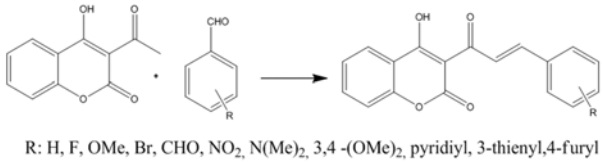


Figure 16. *Claisen condensation reaction.*

4.7. Applied Knoevenagel Condensation of 3-acetyl-4-hydroxycoumarin

Solvent-free conditions for the rapid synthesis of new coumarin derivatives by Knoevenagel condensation under microwave irradiation have been reported by Mladenovic et al. [25]. Different carbonyl derivatives, esters and cyano used for the condensation of 3-acetyl-4-hydroxycoumarin have resulted in varieties of coumarins.

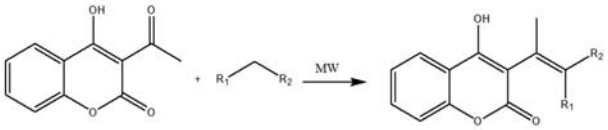


Figure 17. *Knoevenagel condensation reaction.*

4.8. Action of a Ketone in Aqueous Medium

Siddiqui et al. described an environmentally friendly methodology for the above condensation using Zn (L-proline) as the water-recyclable Lewis acid catalyst. In each conversion, the catalyst was successfully recovered and reused several times without significant loss of performance and selectivity [26-27].

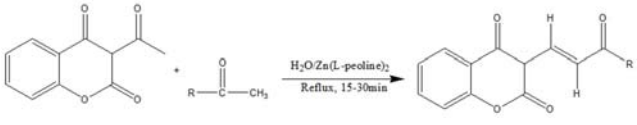


Figure 18. *Action of a ketone in aqueous medium.*

5. Use

3-Acetyl-4-hydroxycoumarin is important as a product and intermediate in analytical, biology and pharmaceutical chemistry.

5.1. Catalytic Use

3-Acetyl-4-hydroxycoumarin is useful for the extraction and separation of uranium from thorium. A significant amount of cerium III and lanthanum can be easily obtained by using 3-acetyl-4-hydroxycoumarin as a complexing agent [28].

5.2. Biological Use

3-Acetyl-4-hydroxycoumarin is able to inhibit the growth of strains of bacteria (Staphylococcus aureus (ATCC 25925), S. aureus (clinical isolate, IHP), Escherichia coli (ATCC 25922), Micrococcus lysodeikticus (ATCC 4698), Bacillus subtilis (clinical isolate, IHP) and Klebsiella pneumoniae (clinical isolate, IHP)) and a strain of fungi (Candida Albicans (ATCC 10259)) [26].

5.3. Pharmaceutical Use

3-acetyl-4-hydroxycoumarin represent the basic structure of several drugs including anticoagulants such as warfarin or acenocoumarol, novobiocin and chlorobiocin used as coumarin antibiotics of natural origin, which are DNA inhibitors [29]. The antiviral activity of single coumarins is primarily focused on inhibiting HIV protease. Recent advances in the development of coumarin derivatives as potent anti-HIV agents, concerning the discovery, structural modification and studies of structure-activity relationships, have been the subject of various reviews or updated articles [30].

6. Synthesis Strategy Applicable to 3-acyl-4-hydroxycoumarins

The coumarins obtained exhibit a structure of an α, β unsaturated lactone and substituted in the α position by the acyl group and in the β position by a two-hydroxide group of high reactivity.

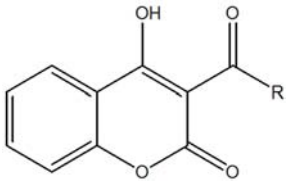


Figure 19. *Structure of 3-acyl-4-hydroxycoumarin.*

Such skeletons can undergo various transformation leading to more complex structures. Among these transformations, the O-acylation reaction (Figure 20) seems to be an interesting way to introduce functional groups capable of cyclizing or not and giving rise to multi-cyclic compounds.

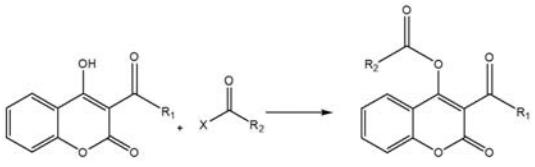


Figure 20. *O-acylation of 3-acyl-4-hydroxycoumarins.*

The synthesized 3-acyl-4-hydroxycoumarin with a structure similar to 3-acetyl-4-hydroxycoumarin could undergo different transformations applied to the latter. Indeed, the acetylation reaction of 3-acyl-4-hydroxycoumarin will introduce an acetyl group on the alcohol function of our compounds.

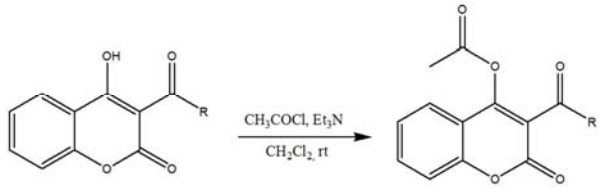


Figure 21. *Acetylation reaction of 3-acyl-4-hydroxycoumarin.*

Several other syntheses can be considered, in particular:

1) The bromination reaction of 3-acyl-4-hydroxycoumarins,
2) The reduction reaction of 3-acyl-4-hydroxycoumarins,
3) The methylation reaction of 3-acyl-4-hydroxycoumarins,
4) The condensation reaction of 3-acyl-4-hydroxycoumarins,
5) The Knoevenagel condensation reaction,
6) The reaction between 3-acyl-4-hydroxycoumarins and an active methylene species,
7) Etc...

The synthesized molecules can also be submitted to the action of different chemical species seen in the literature

1) Action of diazomethane in acetone
2) Action of acid in ethanol
3) Action of acetic anhydride
4) Action of sulfuric acid
5) Action of soda and ammonia
6) Action of strong base acids on 4-acylisochroman-1,3-diones

7. Conclusion

The presence of a coumarin nucleus will give these species an important pharmacological and therapeutic interest. The literature review presented here indicates that the synthesis and chemical reactivity of 3-acyl-4-hydroxycoumarins could attract the interest of many research groups around the world. Part of the synthetic interest, the known and expected analysis and the biological application of these types of compounds deserves special mention. In view of all that has been seen in this article, C-acyl coumarins, in particular 3-acyl-4-hydroxycoumarins, would offer various synthetic routes to new derivatives that could revolutionize several fields such as health, food, cosmetics, new technologies etc. Finally, I hope this article serves as a stimulus for ongoing research in the field of heterocyclic compound chemistry.

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