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Aldol condensation of 3-acetylcoumarin derivatives and extraordinary side reactions

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Aldol reaction of 3-acetylcoumarin derivatives was explored – a derivative without substituents in the aromatic ring (3-acetylcoumarin) **(1)**, a derivative containing electron withdrawing substituent (3-acetyl-6-nitrocoumarin) **(1a)** and a derivative containing electron donating substituent (3-acetyl-8-methoxycoumarin) **(1b)**. In the first case the typical products of aldol reaction with intact lactone rings were isolated. In the presence of electron donating substituent, a product of aldol reaction was identified, but with opened lactone rings. There was no aldol reaction in the presence of nitro-group and pyran-2-one ring was cleaved.

Key words: 3-acetylcoumarins, aldol reaction, biscoumarins, re-esterification, hemiacetal

INTRODUCTION

The reaction of aldol condensation has been widely used in organic synthesis. In order to synthesize coumarin acidichromic dyes, 7-substituted *3*-acetyl-*4*-hydroxycoumarin has been condensed with *4-N,N*-dimethylaminobenzaldehyde in benzene, giving products of the aldol reaction with very good yields [1].

The reaction of *3*-acetylcoumarin with *3*-pyridylaldehyde in butanol in presence of piperidine gave two products - a product of self aldol condensation and a product of mixed condensation [2].

Different coumarin chalcones have been synthesized by aldol reaction of 3-acetyl-4-hydroxy-8-isopropyl-5-methylcoumarin and 3-acetyl-4-hydroxy-6-chloro-7-methylcoumarin with a variety of aromatic aldehydes with very good yields [3, 4]. Microwave-assisted synthesis has been also used for similar reaction intermediates and synthesis of pyrazolinylcoumarins with possible antioxidant activity [5].

Coumarin chalcones and bis-3-coumarinyl-pyridines have been synthesized by a series of two steps of aldol reactions in solventless conditions [6, 7], using the catalyst $Bi(NO_3)_3$, immobilized on alumina.

The BF_3-catalyzed aldol condensations of 5-methyl-2,3-dihydrofuran The mechanism of formation of hemiacetal group - compound **4** (3-methoxy-3-hydroxy-2-(2'-hydroxy-5'-nitro)-benzylydenebutanoic acid).

-*2*-one with RCHO (R = Ph, halo, nitro, trifluoromethyl, methyl, methoxy or (methylenedioxi)phenyl, thienyl, furyl, cyclohexyl) has given acetyltetrahydrofuranones**,** which show cardiovascular activity [8].

Efficient aldol dimerization of ketones occured when the neat ketone is absorbed on basic Al_2O_3, followed, when necessary, by heating [9]. This could be a reason for forming dimers of acetophenone, *1*-indanone and *1*-tetralone.

Coumarins containing electron withdrawing group (-CN, $-CONH_2$, etc.) at third position and tertiary amino group at seventh position in the coumarin ring, usefull as laser dyes, were prepared by Vilsmeyer formylation of trimethylsililated *3-N,N*-substituted aminophenols, hydrolysis and base-catalyzed aldol condensation with activated methylene compounds [10].

Proline has been used as a catalyst of the aldol reaction for asymmetric direct intermolecular aldol reaction. [11]. Strong solvent influence on the enantiopurity has been observed; anhydrous DMSO has been found to be the most suitable solvent.

4-Hydroxycoumarin has been involved in the aldol type of reaction with benzaldehyde in the presence of NaOH in ultrasonic bath [12]. The product was obtained in high yield.

The aim of the present investigation was to explore the influence of different substituents (electron donating or electron withdrawing) in the benzene ring of 3-acetylcoumarin derivatives on the

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course of the self-aldol condensation and the possible side products.

EXPERIMENTAL

All starting materials were purchased from Merck (Germany), Sigma-Aldrich (USA) and Fluka (Switzerland). They were used without further purification. Melting points were measured in open capillary tubes on a Büchi 535 melting point apparatus (Donau Büchi, Switzerland). The IR spectra were recorded on a Bruker Vertex 70 spectrometer (Bruker, Switzerland) and frequencies were expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Bruker 250 MHz instrument (Bruker, Switzerland) in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard (chemical shifts were reported in ppm units, coupling constants (J) in Hz).

Mass-spectral analysis was performed by electron ionization on a mass-spectrometer Hewlett-Packard 5973 (USA) at 20 eV.

Synthetic procedure

The 3-acetylcoumarin derivative was dissolved in methanol at reflux. The solution obtained was cooled to room temperature and piperidine was added. The reaction mixture was stirred at ambient temperature for 1.5 h and was concentrated *in vacuo*. The product was crystallized from methanol.

Synthesis of 3-[4-oxo-4-(2-oxo-2H-chromene -3-yl)]-2-butene-2-yl-2H-chromene-2-one /1/ /1/ was obtained from 3-acetylcoumarin (3.76 g, 0.02 mol) and piperidine (0.85 g, 1 mL, 0.01 mol). The product was a white amorphous powder. It was recrystallized from isopropyl alcohol.

Synthesis of 3-[2-hydroxy-4-oxo-3-(2-oxo-2H-chromen-3-yl)isobutyl-2H-chromen-2-one /2/

/2/ was crystallized from the same reaction mixture. It was a white-yellow crystal powder and was recrystallized from ethanol.

Synthesis of dimethyl bis [(3-methoxy-2-hydroxy)-benzylidene] - 3-methyl-5-oxo - 3 - heptenoate /3/

/3/ was synthesized from 3-acetyl-8-methoxycoumarin (1.09 g, 0.005 mol) and piperidine 0.0025 mol (0.21 g, 0.3 mL).

The product was a yellow crystal substance. It was recrystallized from isopropyl alcohol.

Synthesis of 3-methoxy-3-hydroxy-2-(2'-hydroxy-5'-nitro)-benzylydenebutanoic acid /4/

The product /4/ was synthesized from 3-acetyl-6-nitrocoumarin (0.37 g, 0.002 mol) and 0.001 mol (0.09 g, 0.1 mL) of piperidine. The crude product was isolated after removing the methanol and mixing of the viscous substance with water.

The final product was a red - orange amorphous mass. It was recrystallized from water.

The physical and spectral properties of the synthesized compounds are presented in Table 1.

Computational chemistry

All calculations were made with the aid of Horseshoe computer cluster (University of Southern Denmark, Odense). The DFT (Density Functional Theory) calculations about geometry optimization and ESP (Electrostatic Potential) charges were implemented by Gaussian 03 program [13]. B3LYP [14-16] /6-31G(d,p) method was used for geometry optimisation and ESP charges calculations. Gauss View program was used to visualize the results from the calculations.

All initial optimizations and conformational search were implemented by Chem-3-D from ChemOffice package [17], using the MM2 force field.

RESULTS AND DISCUSSION

The aim of this investigation was to study the influence of different types of functional groups on the course of aldol condensation.

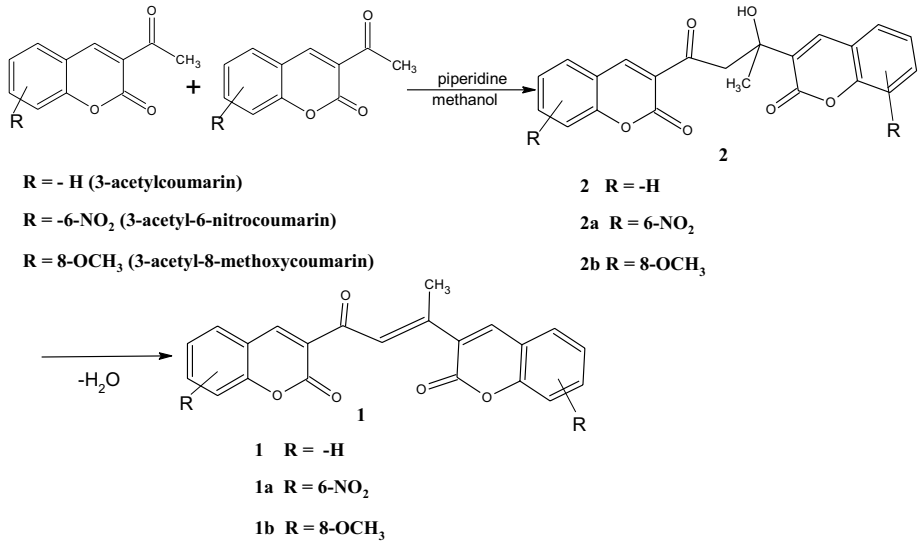
Aldol type of reactions were carried out between two molecules of 3-acetylcoumarin derivatives. The reaction conditions include methanol as solvent and room temperature. The starting compounds were differently substituted 3-acetylcoumarins (3-acetylcoumarin, 3-acetyl-6-nitrocoumarin, 3-acetyl-8-methoxycoumarin), which underwent self condensation to aldol type biscoumarin compounds (**2, 2a** and **2b**). The latter were dehydrated to unsaturated biscoumarin derivatives (**1, 1a** and **1b**). The interaction scheme of the aldol reaction is shown in **Scheme 1.**

The probable products are:

3,3'-[*1*-oxobut-*2*-ene-*1,2*-diyl]-bis(*2H*-chromene-*2*-one) /**1**/; *3,3'*-[*1*-oxobut-*2*-ene-*1,2*-diyl]-bis(6-nitro-*2H*-chromene-*2*-one) /**1a**/; *3,3'*-[*1*-oxobut-*2*-ene-*1,2*-diyl]-bis(8-methoxy-*2H*-chromene-*2*-one) /**1b/.**

These compounds are very convenient for further Michael reaction, because of the activated double bond in one of the coumarin rings.

The biscoumarin derivative /1/ was synthesized according to the above mentioned reaction and its structure was proved by spectral methods (IR, MS) and elemental analysis.



Scheme 1. Aldol reaction and crotonization of 3-acetylcoumarin derivatives

Its structure was also elucidated by DFT (Density Functional Theory) methods. Optimization with B3LYP/6-31G (d,p) method and calculation of the ESP (Electrostatic Potential) charges were made. The geometry of the molecule with the charges is presented in **Fig. 1.** Both coumarin rings are planar, all valent angles are close to 120^0 (116 - 127^0). The valent angles of the side chain are between 125 – 129^0, corresponding to a sp^2-hybrid state of the carbon atoms. The distances: C14 – C15 (C = C) 1.35 Å, C14 – C12 1.48 Å and carbonyl C12 – O39 1.23 Å are signs for π-π conjugation between the π - electrons of the carbonyl bond and π-electrons of the double C = C bond. This π-π conjugation is the reason for distributing the electronic density and concentrating the substantial positive charge on C15 (0.362).

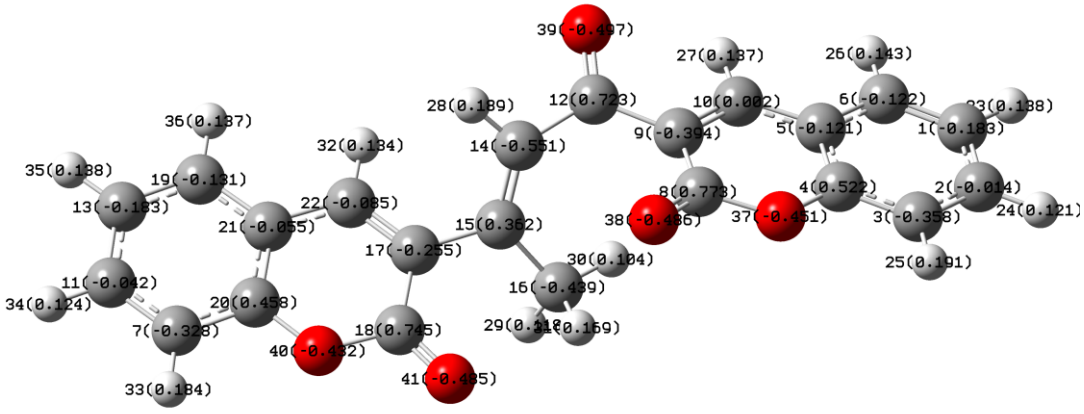
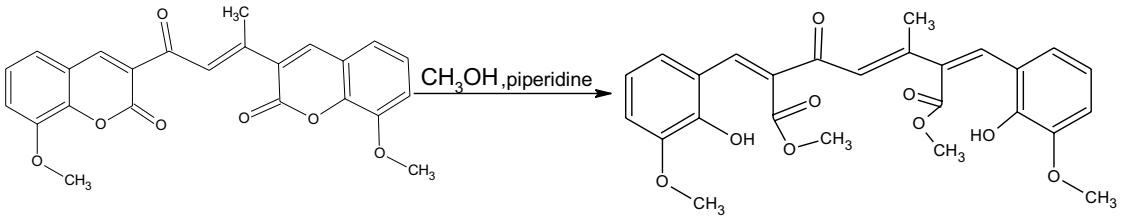


Fig. 1. Optimized structure and ESP charges of the compound /**1**/ with B3LYP/6-31G(d,p) level of theory

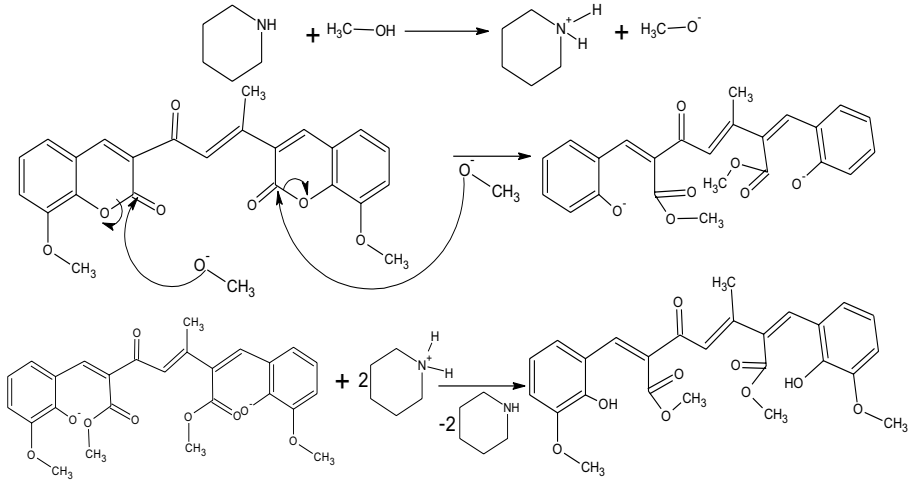
Reactions of nucleophilic additions (for example Michael reaction) will take place at the C15 atom in comparison to the activated C=C from the pyran ring next to the carbonyl group. The π-π conjugation in the pyran ring is much weaker and there is almost zero charge at C10 and slightly negative charge at C22.

From the same reaction mixture a compound /**2**/ (3,3'-(3-hydroxy-1-oxobutane-1,3-diyl)bis(2*H*-chromen-2-one) was isolated with aldol structure which did not undergo an elimination step.

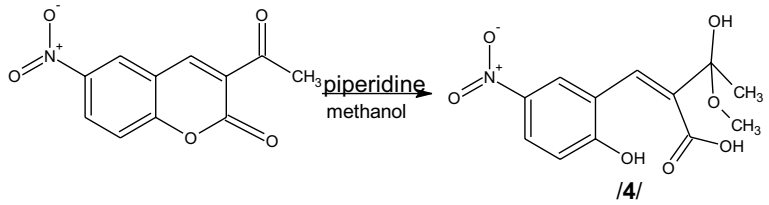
Concerning the compound /**1b**/ obtained from 3-acetyl-8-methoxycoumarin, there is a re-esterification reaction after aldol condensation, which is leading to opening of the lactone ring. The process of re-esterification with methanol was detected by the presence of methyl esters. The general equation of re-esterification of the biscoumarin derivative /**1b**/ to /**3**/ (dimethyl 2,6-bis (2-hydroxy-3-methoxyben-zylidene)-3-methyl-5-oxohept-3-enedioate) is expressed on **Scheme 2**.



Scheme 2. The reaction of re-esterification of the compound **(1)** to **3** (dimethyl bis [(3-methoxy-2-hydroxy)-benzylidene]-3-methyl-5-oxo-3-heptenoate).

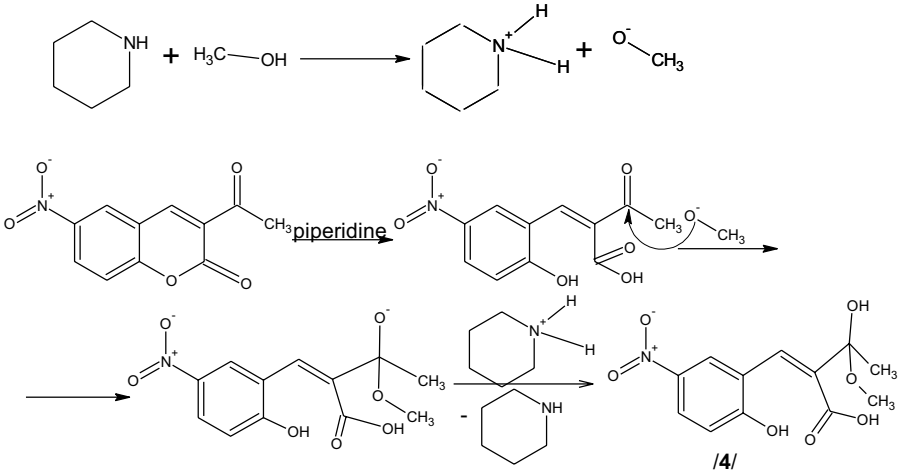


Scheme 3. Mechanism of re-esterification of the compound **3.**



/**4**/

Scheme 4. Mechanism of hydrolysis of lactone group



/**4**/

Scheme 5. The mechanism of formation of hemiacetal group - compound **4** (3-methoxy-3-hydroxy-2-(2'-hydroxy-5'-nitro)-benzylydenebutanoic acid).

Probably, piperidine acts as a base which deprotonates the methanol to a methoxide ion. Thus obtained methoxide ion reacted as a nucleophile, attacked the carbonyl carbon from the lactone ring and opened it. The pyrane-*2*-one rings were transformed to methyl ester group and a phenol group was changed to a phenoxide anion. The latter accepts protons from the piperidinium cation and gives back a phenol hydroxyl group, thus a methyl ester being formed. The mechanism of re-esterification for the compound **/3/** (dimethyl 2,6-

bis (2-hydroxy-3-methoxybenzylidene)-3-methyl-5-oxohept-3-enedioate) **i**s presented in **Scheme 3.**

No aldol condensation with 3-acetyl-6-nitrocoumarin was performed at all.

There was a reaction of hydrolysis and opening of the lactone ring caused by the basic medium of piperidine. The product is a carboxylic acid containing phenolic group at ortho-position in the aromatic ring. The next step was probably the formation of a methoxide anion, caused by the interaction of piperidine and methanol. Methoxide anion is a strong nucleophile, which attacks and adds to the acetyl carbonyl carbon atom /nucleophilic addition/. In the last step, the protonated piperidine gives its proton, thus the hemiacetal group being formed.

The equation and the probable mechanism of formation of the hemiacetal group - compound /**4/** (3-hydroxy-2-(2-hydroxy-5-nitrobenzylidene)-3-methoxybutanoic acid) are presented in **Schemes 4 and 5.**

CONCLUSIONS

On the basis of the experiments it may be concluded that aldol reaction between two molecules of 3-acetylcoumarin derivatives takes place without any side reactions only when starting from 3-acetylcoumarin non-substituted in the aromatic ring. If there is a methoxy-group (electron donating) at the eighth position in the coumarin ring, a reaction of re-esterification and opening of the lactone ring takes place. If there is a nitro-group (strong electron withdrawing substituent) at sixth position, no aldol interaction is observed. In that case there is only cleavage of the lactone ring, formation of methoxide anion and nucleophilic addition of that anion to the carbonyl group from the acetyl fragment. Finally the hemiacetal structure is observed.

The electron donating substituent in the aromatic ring may facilitate the aldol reaction, but the presence of an electron withdrawing substituent impedes that reaction.

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АЛДОЛНА КОНДЕНЗАЦИЯ НА ПРОИЗВОДНИ НА 3-АЦЕТИЛКУМАРИНА С НЕОЧАКВАНИ СТРАНИЧНИ РЕАКЦИИ

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(Резюме)

Изследвана е алдолната реакция на производни на 3-ацетилкумарина – съединение без заместител в ароматното ядро (3-ацетилкумарин) (**1**), с електроноакцепторен заместител (3-ацетил-6-нитрокумарин) (**1a**) и с електронодонорен заместител (3-ацетил-8-метоксикумарин) (**1b**). При използването на 3-ацетилкумарин се изолират типични продукти на алдолната реакция с непроменен лактонов цикъл. Наличието на електронодонорен заместител в ароматното ядро продуктът на алдолната реакция е с отворен лактонен пръстен. Когато в ароматното ядро има електроноакцепторен заместител (нитро група) алдолна кондензация не протича и изходните продукти остават непроменени.