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# Waste waters of milk and cheese processing as an efficient promoter for the synthesis of 1,8-dioxo-octahydroxanthenes

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Waste waters of agricultural and industrial processing have been recently employed to effectively promote numerous "classic" and innovative processes of synthetic organic chemistry. Such a green chemical approach allowed to bypass the use of toxic, polluting, and hazardous chemicals and in the meantime led to an increase of the commercial values of such byproducts. Xanthenes are a group of natural and semi-synthetic compounds with great pharmacological potentialities, also used for several other applications. In this paper we described a new and improved methodology for the synthesis of the title compounds using waste waters of milk and cheese processing as a solvent. 1,8-Dioxo-octahydroxanthenes were obtained in very good yields (94 – 98 %) from differently substituted aromatic aldehydes and dimedone as substrates. Although several reports about the synthesis of 1,8-dioxo-octahydroxanthenes have been published in recent years, this is the first report about the use of waste waters of agricultural and industrial processing to this aim. The findings depicted herein underline once again the great usefulness of agricultural and food industry byproducts to perform green chemical processes.

**Keywords:** Aromatic aldehydes, Dimedone, Green chemistry, Waste waters, Xanthenes

## INTRODUCTION

Modern tendencies of synthetic organic chemistry involve the use and development of greener and more eco-friendly methodologies as an alternative to toxic, hazardous, polluting, and expensive substrates, reagents, and solvents. Recent reports from the literature indicate that numerous organic processes have been accomplished in water, as a safe and inexpensive solvent [1]. In the meantime the use of waste waters derived from agricultural and industrial processing has gained more and more interest of several research teams. Waste waters are in fact able to effectively play the role of promoters and solvents; they have environmentally beneficial features, are non-hazardous, non-toxic, non-polluting, largely available, and in general cheap. Examples of organic reactions employing waste waters include the Knoevenagel condensation [2], the Biginelli reaction [3], the preparation of amides [4], the reduction of carbonyls, the hydrolysis of esters and amides [5[ and several others, most of which have been recently extensively reviewed [6]. The xanthene core is found in several natural products. Furthermore, xanthenes semisynthetic derivatives exert also a wide array of promising pharmacological activities as anti-inflammatory [7], anti-depressant, and anti-malarial agents [8]. They are also used as dyes and fluorescent probes [9, 10]. Reported methodologies for the synthesis of title compounds typically include the condensation of aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione, commonly known as dimedone, in the presence of different catalysts like $ZnCl_2$/choline chloride [11], ZnO/$CH_3COCl$ [12], Amberlyst-15 [13], $ZrOCl_2$ hydrate [14], trichloroisocyanuric acid [15], silica sulfuric acid [16], nanosized MCM-41-$SO_3H$ [17], $Fe_3O_4$ nanoparticles [18], ionic liquids like [bmim][$HSO_4$] [19, 20] [hmim]TFA [21] [TMPSA][$HSO_4$] [22], [DDPA][$HSO_4$] [23], [$Et_3N$-$SO_3H$]Cl [24], [Hbim]$BF_4$ [25], tetramethylguanidium trifluoroacetate [26], [BPy][$HSO_4$] [27], ammonium hydrogen sulphate based ionic liquid immobilized on $Na^+$-montmorillonite [28], $CuCl_2$ [29] titanium aminophosphonates [30], cesium phosphotungstate [31] and natural phosphates [32]. However, the majority of methodologies for the synthesis of 1,8-dioxo-octahydroxanthenes is featured by several drawbacks and disadvantages like low yields (often strictly depending on the structures of the starting materials), long reaction times, high temperatures, use of hazardous and expensive catalysts, tedious work-up procedures, non recyclability of catalysts and solvents. Thus, development and set up of greener protocols to provide 1,8-dioxo-octahydroxanthenes can be still considered a challenging field of research in synthetic organic chemistry. As a continuation of our studies aimed at settling easy to handle methods to obtain synthons and compounds of biological interest using a green technology, we report herein that 1,8-dioxo-octahydroxanthenes can be efficiently and

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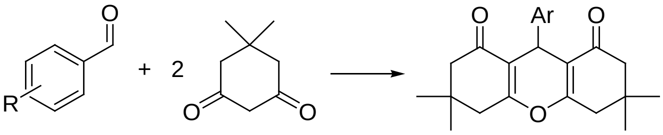


**Scheme 1**. Synthetic route to 1,8-dioxo-octahydroxanthenes

selectively obtained by coupling of dimedone and different functionalized benzaldehydes using waste waters derived from milk and cheese processing (Scheme 1).

## EXPERIMENTAL

Waste waters of milk processing have been obtained by local farmers.

*General procedure:* Benzaldehyde (1.0 mmol) and dimedone (1.01 mmol) were suspended in an aqueous medium (3 mL). The resulting mixture was let to react at 50 °C overnight. The precipitate so formed was filtrated under vacuum. Structural assignments (NMR) were made by comparison of the recorded analytical data with those of commercially available samples or those already reported for the same compounds.

*Coumarin-3-carboxylic acid* (entry 1): white solid (m.p.: 189-191 °C). Analytical data were in full agreement with those recorded for a pure commercial sample.

*7-(Diethylamino)coumarin-3-carboxylic acid* (entry 2): yellowish solid (m.p.: 221-223 °C). Analytical data were in full agreement with those recorded for a pure commercial sample.

*7-Nitrocoumarin-3-carboxylic acid* (entry 3): reddish solid (m.p.: 233-235 °C). Analytical data were in full agreement with those already reported in the literature for the same compound [33].

*6-Bromocoumarin-3-carboxylic acid* (entry 4): reddish solid (m.p.: 214-215 °C). Analytical data were in full agreement with those already reported in the literature for the same compound [16].

*6-Hydroxycoumarin-3-carboxylic acid* (entry 5): white solid (m.p.: 280-282 °C). Analytical data were in full agreement with those already reported in the literature for the same compound [16].

*4-Methyl-6-nitrocoumarin-3-carboxylic acid* (entry 6): reddish solid (m.p.: 244-247 °C). Anal. Calc. for $C_{11}H_7NO_6$: C 53.02, H 2.83, N 5.62, O 38.52; Found: C 53.09, H 2.77, N 5.60, O 38.44. $^1$H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H), 6.05 (s, 1H), 7.74-8.23 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 18.9, 111.6, 118.5, 125.9, 127.9, 133.7, 138.6, 154.4, 156.5, 160.2.

*6-Chloro-4-methylcoumarin-3-carboxylic acid* (entry 7): brownish solid (m.p.: 223-247°C) Analytical data were in full agreement with those already reported in the literature for the same compound.[16]

*7-Methoxy-4-methylcoumarin-3-carboxylic acid* (entry 8): yellowish solid (m.p.: 183-185 °C). Analytical data were in full agreement with those recorded for a pure commercial sample.

*6-Hydroxy-4-methylcoumarin-3-carboxylic acid* (entry 9): pale yellow solid (m.p.: 201-202 °C). Analytical data were in full agreement with those recorded for a pure commercial sample.

*6,8-Dihydroxy-4-methylcoumarin-3-carboxylic acid* (entry 10): pale yellow solid (m.p.: 246-248 °C d). Anal. Calc. for $C_{11}H_8O_6$: C 55.94, H 3.41, O 40.65; Found: C 55.99, H 3.35, O 40.64. $^1$H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 5.85 (s, 1H), 6.23 (s, 1H), 6.89 (s, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 18.9, 100.4, 106.7, 112.2, 124.9, 132.9, 144.1, 155.0, 156.0, 160.9.

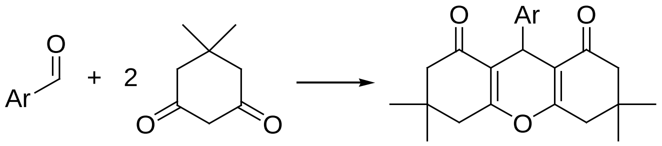
*4-Methylcoumarin-3-carboxylic acid* (entry 11): white solid (m.p.: 161-162 °C). Analytical data were in full agreement with those recorded for a pure commercial sample.

## RESULTS AND DISCUSSION

Preliminary assays to optimize reaction conditions were performed using commercially available benzaldehyde and dimedone as starting materials. Both were suspended in different aqueous media represented by waste waters derived from milk/cheese processing. This solvent was the same we recently used to successfully accomplish the synthesis of cinnamic and coumarin-3-carboxylic acids [35]. Reactions were initially carried out over a period of 18 h under magnetic stirring at room temperature and monitored by thin layer chromatography (TLC). Employing the above depicted experimental conditions, low conversions (<15%) into the desired 1,8-dioxo-octahydroxanthenes were achieved. Thus we decided to increase the temperature up to 50 °C and follow the progress of reactions over the same period. This was seen to be the best medium in promoting the conversion of benzaldehyde and dimedone to the condensed adduct. In fact 1,8(2*H*)-dione,3,4,5,6,7,9-hexahydro-3,3,6,6-tetramethyl-9-phenyl-1*H*-xanthene was obtained as a yellow solid after filtration under vacuum in 97 % yield without the need of any other purification. It is noteworthy to underline that a blank experiment using distilled water alone as the solvent applying temperatures in the range of 30 °C– 90 °C led to virtually no progress of the reaction. Handling these excellent results, we decided to use waste waters of milk/cheese processing and 50 °C as the optimized reaction conditions to validate the protocol and apply it to the condensation of different substituted aromatic aldehydes with dimedone. Results are reported in Table 1. Substrates with electron donating or electron withdrawing groups reacted to the same extent providing the desired 1,8-dioxo-octahydroxanthenes in very high yields. For all entries, final products were simply collected as solids after filtration under vacuum from the reaction media without the need of any chromatographic purifications. Waste waters were recovered as filtrates from every synthetic step, recycled and re-used to carry out other condensations without appreciable loss of effectiveness in terms of yields of the desired xanthene derivative. For example, reactions leading to 1,8(2*H*)-dione,3,4,5,6,7,9-hexahydro-3,3,6,6-tetramethyl-9-(4'-methoxy)phenyl-1*H*-xanthene (entry 2) and 1,8(2*H*)-dione,3,4,5,6,7,9-hexahydro-3,3,6,6-tetramethyl-9-(4'-methoxy) phenyl-1*H*-xanthene (entry 5) were accomplished four successive times each and provided adducts with yield values ranging from 93 % to 96 %. To rationalize the efficiency of waste waters of milk processing as promoters of the title condensation process, we may hypothesize that this medium has a suitable acidic pH value (due the presence of organic acids like pyruvic and lactic ones) to promptly boost the reaction between aromatic aldehydes and dimedone. Indeed, pH measurement for the employed waste waters recorded a value of 4.62. Although we previously found that application of ultrasound was seen to be an efficient means for the condensation of differently substituted acetophenones and benzaldehydes to provide coumarin-3-carboxylic and cinnamic acids in high yields in 5 – 15 min, the same protocol was not equally effective for the synthesis of 1,8-dioxo-octahydroxanthenes.

As a conclusion, in this paper we showed that safe, non polluting, cheap, and easy to obtain and handle waste waters derived from milk and cheese processing represent a powerful means to promote an efficient and high-yielding condensation reaction of differently substituted aromatic aldehydes with dimedone leading to 1,8-dioxo-octahydroxanthenes. Favourable features of our method include a simple work-up, mild conditions and very good yields. Furthermore, although numerous methodologies for the synthesis of the title compounds appeared in the literature during the last two decades, this is the first time that waste waters are employed to promote the process. Thus, the reaction described herein can be viewed as an additional and alternative example in the field of 1,8-dioxo-octahydroxanthenes synthesis. The use of water residues of industrial processing can be considered as an example of useful waste management and recycling. Further investigations to extend the scope and applicability of waste waters and related solvents are now in progress in our laboratories and will be reported in due course.

**Table 1.** Synthesis of 1,8-dioxo-octahydroxanthenes from waste waters of milk processing



| Entry | Ar | Yield (%)[a] |
|---|---|---|
| 1 | $C_6H_5$ | 97 |
| 2 | 4-$CH_3O$-$C_6H_4$ | 98 |
| 3 | 4-$CH_3$-$C_6H_4$ | 95 |
| 4 | 4-OH-$C_6H_4$ | 96 |
| 5 | 4-F-$C_6H_4$ | 96 |
| 6 | 4-$NO_2$-$C_6H_4$ | 97 |
| 7 | 4-Cl-$C_6H_4$ | 98 |
| 8 | 4-Br-$C_6H_4$ | 98 |
| 9 | 4-OH-3-$CH_3O$-$C_6H_3$ | 95 |
| 10 | 3-$NO_2$-$C_6H_4$ | 94 |
| 11 | 3-$CH_3O$-$C_6H_4$ | 95 |
| 12 | 2-Cl-$C_6H_4$ | 94 |
| 13 | 2,4-$Cl_2$-$C_6H_3$ | 98 |
| 14 | 2-OH-$C_6H_4$ | 96 |
| 15 | $C_6H_5$-CH=CH | 97 |

[a] Yields of pure isolated products, characterized by $^1$H NMR, $^{13}$C NMR, elemental analysis, and melting point. Analytical data of all adducts exactly matched those already reported for the same compounds [14, 15, 19, 20, 24, 27].

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# ОТПАДЪЧНИ ВОДИ ОТ ПРОИЗВОДСТВОТО НА МЛЯКО И СИРЕНЕ КАТО ЕФЕКТИВЕН ПРОМОТОР ЗА СИНТЕЗА НА 1,8-ДИОКСО-ОКТАХИДРОКСАНТЕНИ

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(Резюме)

Отпадни води от селскостопански и промишлени производства се използват в последно време за подпомагане на голям брой класически и иновативни процеси в синтетичната органична химия. Такъв „зелен" химичен подход позволява да се избегне използването на токсични, замърсяващи и опасни химикали, като същевременно води до повишаване на търговската стойност на такива странични продукти. Ксантените са група природни и полусинтетични съединения с голям фармакологичен потенциал и редица други приложения. В настоящата статия е описана нова, подобрена методология за синтез на 1,8-диоксо-октахидроксантени чрез използване на отпадна вода от производството на мляко и сирене като разтворител. 1,8-Диоксо-октахидроксантените са получени с много добри добиви (94 – 98 %) от различно-заместени ароматни алдехиди и димедон като субстрати. Въпреки публикуването на редица статии върху синтеза на 1,8-диоксо-октахидроксантени през последните години, настоящото съобщение е първото, в което за целта се използва отпадна вода от селскостопанско и промишлено производство. Това подчертава още веднъж ползата от страничните продукти на селскостопански и промишлени производства за осъществяването на „зелени" химични процеси.